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Fully Stereocontrolled Syntheses of 3-Oxacarbacyclin and Carbacyclin by the Conjugate Addition-Azoalkene-Asymmetric Olefination Strategy

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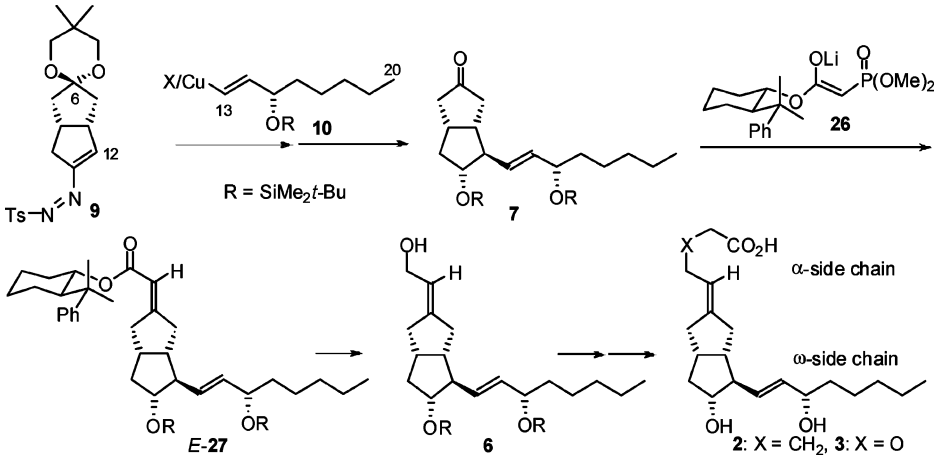

A fully stereocontrolled synthesis of 3-oxacarbacyclin (**3**) and a formal synthesis of carbacyclin (**2**) are described. The syntheses are based on the conjugate addition-azoalkene-asymmetric olefination strategy. Its key features are (1) the stereoselective establishment of the complete ω-side chain of **2** and **3** through conjugate addition of the enantiopure C13−C20 alkenylcopper derivative **10** to the enantiopure C6−C12 bicyclic azoalkene **9** and (2) the 5*E*-stereoselective construction of the α-side chain through a Horner−Wadsworth−Emmons olefination of the bicyclic ketone **7** with the chiral lithium phosphonoacetate **26** with formation of ester *E*-**27**. The allylic alcohol **6** serves at late stage as the joint intermediate in the synthesis of **2** and **3**.

Introduction

Prostacyclin (**1**) (Figure 1) has attracted the attention of chemistry, biology, and medicine ever since its discovery in 1976 by Vane et al.[1] It is the strongest endogenous inhibitor of blood platelet aggregation and a strong vasodilator. Prostacyclin plays an important role not only in the vascular and central nervous system but also in inflammation. Studies of prostacyclin and its medicinal application are hindered, however, by short chemical and metabolic half-lives. While the chemical instability of prostacyclin is caused by a fast hydration of the enol ether moiety even under physiological conditions, the metabolic instability is due to a rapid oxidation in the β-position to the carboxy group, leading finally to a degradation of the α-side chain. The carbocyclic analogous carbacyclin (**2**)[2] and iloprost (**4**)[1d,2b−e] are chemically stable and strong agonists. They have turned out to be excellent probes for the elucidation of the biological functions of prostacyclin and structure of its receptors.[3] Moreover, iloprost is a valuable drug for the treatment of vascular obliterative deceases and pulmonary hypertension.[1d,4] Although carbacyclin and iloprost are chemically much more stable than **1**, they still suffer a rapid metabolization via β-oxidation of the α-side chain. 3-Oxacarbacyclin (**3**)[5c,6] and 3-oxailoprost (**5**)[7,8] are expected to have a higher metabolic stability because of the inhibition of the β-oxidation by the oxygen atom in 3-position.[9,10] Generally, the most challenging problems in the synthesis of **2** and **3** are the stereoselective establishment of both the hydroxy group at C15 and the exocyclic double bond at C5.[2,11] The synthesis of **2** and **3**, which

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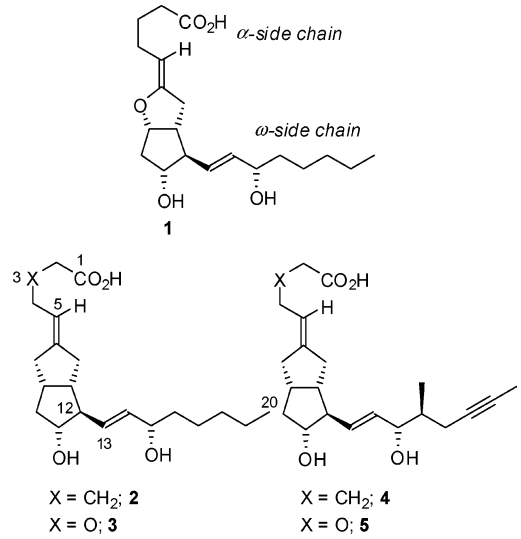

FIGURE 1. Prostacyclin and carbacyclins.

we had described previously, failed to accomplish stereocontrol at C15.[5c,6,12] Recently, we have developed a new and common strategy for the fully stereocontrolled synthesis of iloprost (**4**) and 3-oxailoprost (**5**).[7] Its key steps are (1) the establishment of the complete 15*S*,16*S*-configured ω-side chain through the stereoselective conjugate addition of an enantio- and diastereopure alkenylcopper compound to an enantiopure bicyclic azoalkene, (2) the stereoselective construction of the 5*E*-configured α-side chains via an asymmetric Horner−Wadsworth−Emmons olefination,[5c,6,7,10,14,15] and (3) the establishment of the α-side chain of **4** through a highly selective allylic alkylation. We now describe a fully stereocontrolled synthesis of 3-oxacarbacyclin (**3**) and a formal synthesis of carbacyclin (**2**) by the conjugate addition-azoalkene-asymmetric olefination strategy. The successful syntheses of **2** and **3** together with the previous ones of **4** and **5** demonstrate that this strategy allows a general access to carbocyclic prostacyclin analogues.[16,17]

Results and Discussion

Retrosynthesis. The retrosynthetic analysis of **2** and **3** called for the conjugate addition of the C13−C20 alkenylcopper derivative **10** to the C6−C12 bicyclic azoalkene **9** with formation of hydrazone **8** and the chemo- and stereoselective conversion of the latter to ketone **7** (Scheme 1). Ketone **7** has already served as an intermediate in a number of unselective syntheses of carbacyclin (**2**).[2,18] The crucial 5*E*-stereoselective construction of the α-side chains of **2** and **3** ought to be accomplished via an asymmetric HWE-olefination of **7**, leading finally to the allyl alcohol **6**. Alcohol **6**, which is obtained at a late stage, is thus planned to be the joint intermediate in the synthesis of **2** and **3**. The final steps on route from **6** to **2** and **3** include a regio- and stereoselective allylic alkylation and an etherification, respectively. Transformations of this type have already been successfully implemented in the syntheses of **4** and **5** starting from a structurally closely related allylic alcohol.[7]

Asymmetric Synthesis of Building Blocks. Azoalkene **9** of 96% ee was obtained in 50% overall yield starting from the readily available achiral bicyclic ketone **11**[19] via the intermediates **12**−**14** (Scheme 2).[7,20] The key step of the synthesis of **9**

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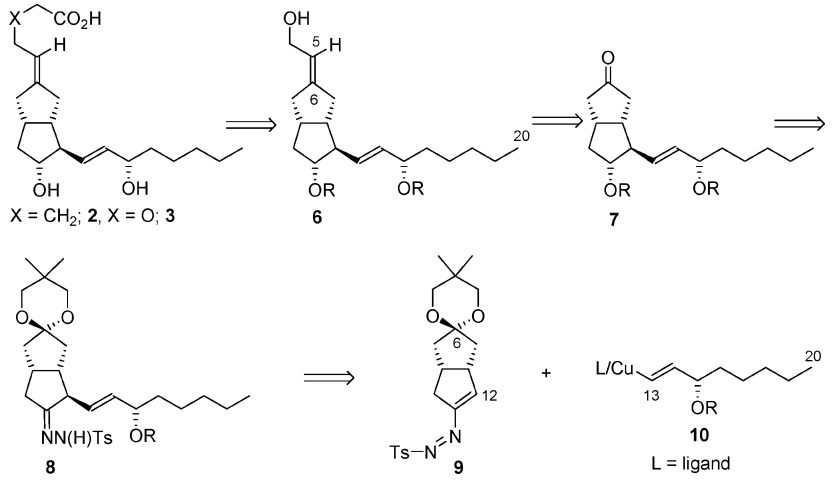
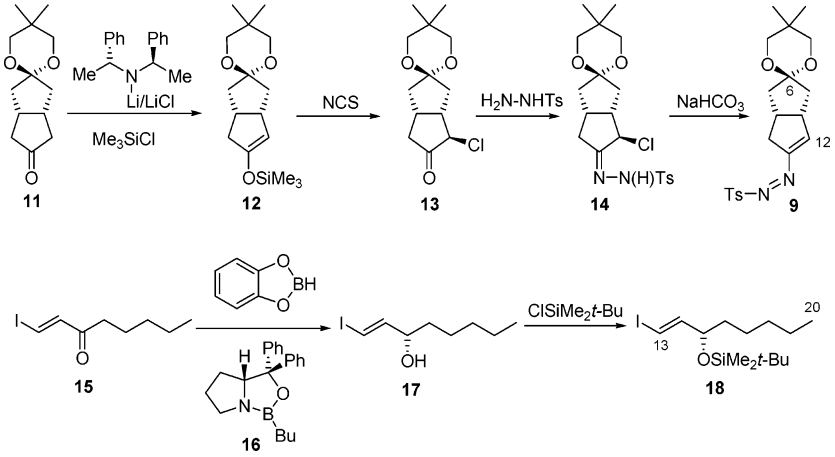
SCHEME 1. Retrosynthesis of Carbacyclin and 3-Oxacarbacyclin Based on the Conjugate Addition-Azoalkene-Asymmetric Olefination Strategy



SCHEME 2. Asymmetric Syntheses of the C6−C12 and C13−C20 Building Blocks



is the efficient desymmetrization of the ketone through deprotonation with the chiral base in the presence of $ClSiMe_3$, leading to the formation of the enol ether **12**.[6,7,20,21]

Several different enantioselective syntheses of the alkenyl iodide **17**, which is a key intermediate in the synthesis of prostaglandins,[2a,d] have already been described.[22] We selected for the synthesis of alcohol **17** the catalytic asymmetric reduction of the readily available ketone **15**[22a,23] with catecholborane in the presence of 15 mol % of oxazaborolidine **16**.[22d] Thereby the alcohol of 96−98% ee was obtained in 95% yield. A high enantioselectivity in the reduction of **15** was only ensured by the slow addition of the ketone to the reducing reagent.[22e] Silylation of alcohol **17** afforded the silyl ether **18** in practically quantitative yield.[24]

Connection of Building Blocks. A crucial step of the synthesis of **2** and **3** is the stereoselective conjugate addition of the alkenylcopper derivative **10** to the azoalkene **9** (Scheme 3). To achieve a high efficiency in the coupling step, it was of importance to apply the two building blocks in a ratio of or close to 1:1. We had previously shown in the case of the synthesis of **4**, **5**,[7] and a 13,14-dinor-interphenylene carbacyclin[20] that this can be accomplished by using alkenyl- and arylcopper reagents derived from the corresponding lithiumorganyls and either CuI/PBu_3[25a] or CuCN/2LiCl.[25b] Lithiation of iodide **18** with BuLi gave the alkenyllithium derivative **20**[26] that was converted to the alkenylcopper derivative **10** upon treatment with 1.05 equiv of CuCN and 2.12 equiv of LiCl in THF. Surprisingly, treatment of the alkenylcopper reagent **10** with 0.81 equiv of azoalkene **9** afforded hydrazone **8** only in low yields. It was eventually found that an efficient and

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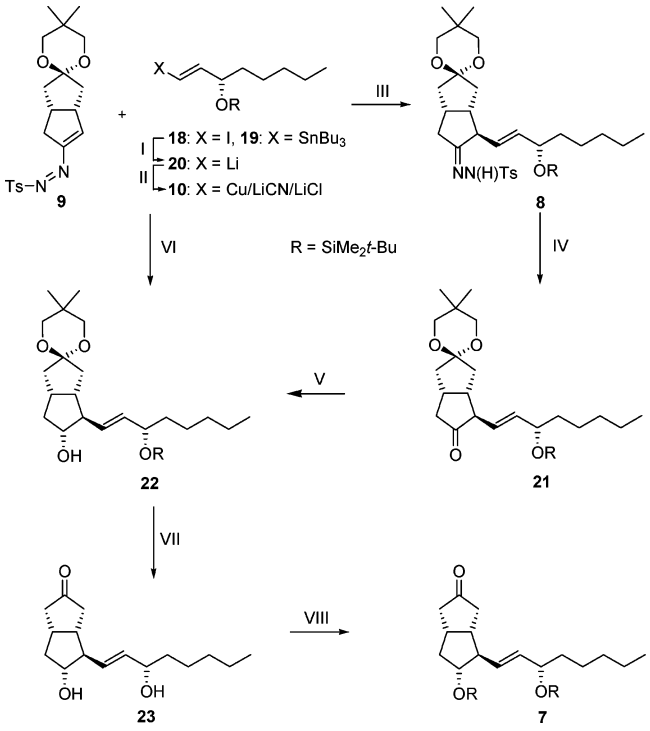
SCHEME 3. Conjugate Addition of Alkenylcopper Derivative 10 to Azoalkene 9[a]

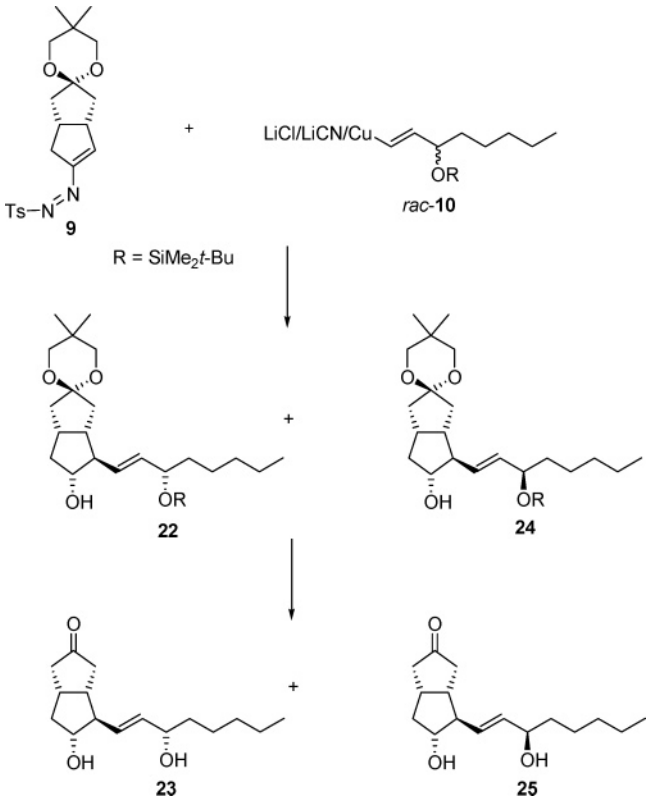


[a] Reagents and conditions: (I) 0.98 equiv of BuLi, THF, −78 °C, 1 h. (II) **20**, 1.1 equiv of CuCN×2LiCl, THF, −78 °C, 30 min (method A) or **20**, 2.2 equiv of CuCN×2LiCl, THF, −78 °C, 30 min (method B). (III) (a) 1.2 equiv of **10**, **9**, 1.3 equiv of CuCN×2LiCl, THF, −78 °C, 30 min (method A) or 1.2 equiv of **10**, **9**, THF, −78 °C, 30 min (method B); (b) 1.2 equiv of Bu_3SnCl, −78 °C, 15 min; (c) NH_4Cl/NH_3 (9:1), −78 °C to rt. (IV) 20 equiv of cyclohexene, 1.05 of equiv $(PhSeO)_2O$, THF, rt, 1 h. (V) 4 equiv of $NaBH_4$, EtOH, −40 °C, 7 h. (VI) (a) 1.2 equiv of **10**, **9**, 1.1 equiv of CuCN×2LiCl, THF, −78 °C; (b) 1.2 equiv of Bu_3SnCl, THF, −78 °C; (c) H_2O, NH_4Cl, THF, −78 °C to rt; (d) 1.05 equiv of $(PhSeO)_2O$, 20 equiv of cyclohexene, THF, rt; (e) 6 equiv of $NaBH_4$, EtOH, 0 °C; (f) H_2O, NH_4Cl, 0 °C to rt. (VII) TsOH, acetone/water, rt, 16 h. (VIII) *t*-$BuMe_2SiCl$, imidazole, DMF, rt.

reproducible conjugate addition of **10** to azoalkene **9** could be achieved by using both building blocks in a ratio of 1.22:1 in the presence of an additional amount of CuCN (1.05 equiv) and LiCl (2.12 equiv). The reaction was carried out either by adding a solution of CuCN/LiCl and azoalkene **9** in THF to a solution of **10** in THF or by adding a THF solution of **10** and CuCN/LiCl to a THF solution of azoalkene **9**. Thereby the diastereomerically pure hydrazone **8** was obtained in 71−73% yield. Quenching of the reaction mixture with Bu_3SnCl led to the isolation of stannane **19**[27] in 29% yield based on iodide **18**. A lithiation of stannane **19** with formation of the alkenyllithium derivative **20** has already been described.[27]

The chemoselective cleavage of hydrazone **8** was achieved by treatment with 1.05 equiv of $(PhSeO)_2O$ in the presence of 20 equiv of cyclohexene, which presumably serves as a radical scavenger.[7,20,28] Because of the lability of **21** on silica gel, the ketone was not further purified but reduced with $NaBH_4$, which gave the diastereomerically pure alcohol **22** in 61% overall yield based on **8**. The synthesis of alcohol **22** has also been carried out without the isolation of hydrazone **8** and ketone **21** in 52% overall yield based on azoalkene **9**. The treatment of acetal **22** with acetone/water and TsOH afforded ketodiol **23**[6,18] in 87% yield after purification by column chromatography. Silylation of diol **23** finally gave the protected ketodiol **7** in 94% yield.

SCHEME 4. Conjugate Addition of the Racemic Alkenylcopper Derivative *rac*-10 to Azoalkene 9[a]



[a] Reagents and conditions: see Scheme 3.

Because of analytical and synthetic reasons, the diastereomeric diols **23** and **25** (Scheme 4) were synthesized starting from azoalkene **9** of 96% ee and the racemic iodide *rac*-**18**. Treatment of **9** with 4 equiv of *rac*-**10**, according to the one-pot reaction sequence described above, finally gave a mixture of alcohols **22** and **24** in a ratio of 1:1 in 62% yield. The mixture of alcohols **22** and **24** was treated with TsOH in acetone/water, which furnished diol **23**[6,18] in 42% yield and diol **25**[18] in 44% yield after separation by column chromatography. A comparison of the ^1H NMR spectra of **23** and **25** with the ^1H NMR spectrum of **23** obtained starting from **9** (96% ee) and **10** (98% ee) showed diol **23** to be pure. This was confirmed by a HPLC analysis of **23**. Thus the purification of **23** by column chromatography had efficiently removed the minor diasteromers *ent*-**25** and **25**, derived from the 2% of *ent*-**9** and 1% of *ent*-**18**, which were contained in azoalkene **9** and iodide **18**, respectively.

Stereoselective Construction of α-Side Chain. For the stereoselective establishment of the α-side chain of **3**, an asymmetric HWE olefination of ketone **7** was selected as the key step. We had already successfully applied an olefination of this type in the synthesis of **4** and **5**[7] and the previous syntheses of **3**.[5b,6] Thus treatment of ketone **7** with 4.3 equiv of the chiral lithium phosphonoacetate **26**[5c,6,7,10,14] in THF at −62 °C for 6 days finally gave a mixture of the diastereomeric esters *E*-**27** and *Z*-**27** in a ratio of 95:5 in 88% yield (Scheme 5).

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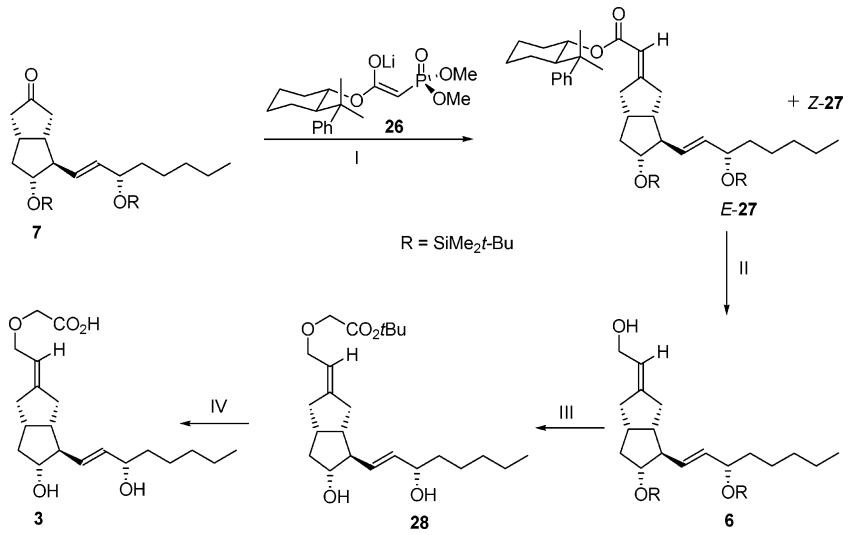
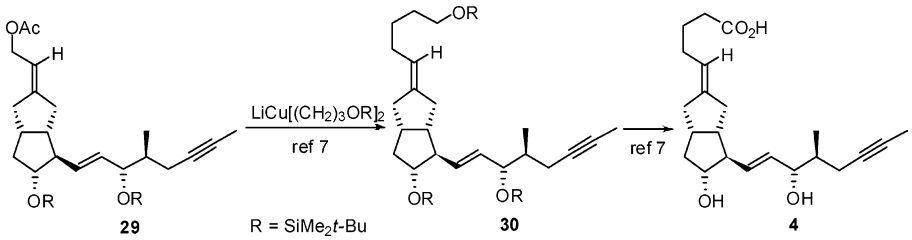
SCHEME 5. Asymmetric Olefination and Completion of the Synthesis of 3-Oxacarbacyclin (3)[a]



[a] Reagents and conditions: (I) (a) 4.4 equiv **26**, THF, −62 °C, 6 d; (b) NH_4Cl, −62 °C to rt; (c) HPLC. (II) (*i*-Bu)$_2$AlH, THF, 0 °C. (III) (a) Bu_4NHSO_4, 50% NaOH, $BrCH_2COOt$-Bu, CH_2Cl_2, rt; (b) Bu_4NF, THF, rt. (IV) MeOH, 1 N NaOH, NaH_2PO_4, pH 4−5, rt.

SCHEME 6. 5*E*-Stereoselective Synthesis of Iloprost via Allylic Alkylation[7]



Preparative HPLC afforded ester *E*-**27** of ≥99% de in 81% yield. The reduction of ester *E*-**27** with (*i*-Bu)$_2$AlH in THF gave the allylic alcohol **6** in 88% yield. The treatment of alcohol **6** with an excess of $BrCH_2COOt$-Bu and 50% aqueous NaOH in CH_2Cl_2 in the presence of Bu_4NHSO_4 followed by the desilylation of the corresponding bissilyl ether with Bu_4NF furnished the dihydroxy ester **28** in 89% overall yield. Finally, the hydrolysis of ester **13** with NaOH in MeOH and protonation of the corresponding carboxylate salt with NaH_2PO_4 to pH 4−5 afforded 3-oxacarbacyclin (**3**)[5b,6] in 90% yield.

The synthesis of the allyl alcohol **6** can be regarded as a formal asymmetric synthesis of carbacyclin (**2**). We had previously described a synthesis of iloprost (**4**), the key step of which is the highly stereo- and regioselective allylic alkylation of the allyl acetate **29** with the C1−C3-organocuprate with formation of silyl ether **30** (Scheme 6).[7] Therefore, it seems safe to assume that the analogous allylic alkylation of the acetate of alcohol **6** will also proceed efficiently to give the corresponding C1−C20 alcohol.

Conclusion

We have described an asymmetric synthesis of 3-oxacarbacyclin (**3**) and a formal synthesis of carbacyclin (**2**), which achieve full stereocontrol of all stereogenic elements. The successful syntheses of carbacyclin, 3-oxacarbacyclin, iloprost, and 3-oxailoprost demonstrate the generality of the conjugate addition-azoalkene-asymmetric olefination strategy for the synthesis of carbacyclins, which takes advantage of the availability of the bicyclic ketone **11** on a large scale.

The alteration of the structure of the ω-side chain of prostacyclin and prostaglandins has turned out to be the most important means for obtaining analogues with high and specific biological activities[2] as shown, for example, by iloprost (**4**).[1d] The prostaglandin synthesis by the conjugate addition-enone strategy[2a,d,29] has made available a large number of structurally different alkenyl iodides and stannanes of the type shown in Figure 2.[30] Further ω-side chain building blocks of this type will be accessible either through an enantioselective reduction of the corresponding iodo and stannyl enones or a hydrozirconation-iodination of the corresponding propargylic alcohols.[30e,31]

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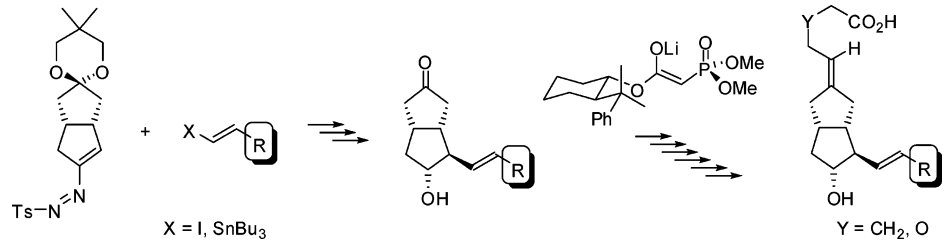

FIGURE 2. Conjugate addition-azoalkene-asymmetric olefination route to carbacyclins and 3-oxacarbacyclins carrying a modified ω-side chain.

Thus, the conjugate addition-azoalkene route should allow the fully stereocontrolled synthesis of a wide range of ω-side chain modified carbacyclins.[7,20]

Experimental Section

(−)-(*E*)-*N*′-((3a′*S*,4′*R*,6a′*R*)-4′-((*S*,*E*)-3-(*tert*-Butyldimethylsilyloxy)oct-1-enyl)-5,5-dimethyldihydro-1′*H*-spiro[[1,3]dioxane-2,2′-pentalene]-5′(3′*H*,6′*H*,6a′*H*)-ylidene)-4-methyl-benzenesulfonohydrazide (8). Method A. BuLi (0.96 mL, 1.6 M in hexanes, 1.54 mmol) was added to a solution of iodide **18** (98% ee, 578 mg, 1.57 mmol) in THF (3 mL) at −78 °C. After the mixture was stirred for 1 h at −78 °C, a cold solution of CuCN (149 mg, 1.66 mmol) and LiCl (141 mg, 3.33 mmol) in THF (2 mL) was added at −78 °C via cannula. The resulting yellow solution was stirred at −78 °C for 30 min. Then a cold solution of azoalkene **9** (ee 96%, 500 mg, 1.28 mmol), CuCN (149 mg, 1.66 mmol) and LiCl (141 mg, 3.33 mmol) in THF (4 mL) was added via cannula, followed by stirring at −78 °C for 30 min. Then Bu_3SnCl (500 mg, 1.54 mmol) was added, followed by stirring at −78 °C for 15 min. Subsequently water (3 mL) was added and the mixture was warmed to room temperature. Then the mixture was diluted with Et_2O (100 mL) and washed with a mixture of saturated aqueous NH_4Cl and concentrated aqueous NH_3 (10:1, 3 × 20 mL). The combined aqueous phases were extracted with Et_2O (3 × 20 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification by chromatography (hexanes/Et_2O, 2:1) gave hydrazone **8** (589 mg, 73%) and stannane **19** (246 mg, 29%). **8**: colorless foam; R_f 0.40 (hexanes/EtOAc, 2:1), $[\alpha]_D$ −39.0 (*c* 1.0, THF). ^{1}H NMR (400 MHz, d_8-THF): δ 0.03 (s, 3 H, $SiCH_3$), 0.07 (s, 3 H, $SiCH_3$), 0.87−0.92 (m, 18 H, $SiC(CH_3)_3$, $C(CH_3)_2$, CH_2CH_3), 1.19−1.55 (m, 8 H), 1.56−1.63 (m, 1 H), 1.75−1.82 (m, 1 H), 2.08−2.29 (m, 4 H), 2.37 (s, 3 H, $PhCH_3$), 2.44−2.63 (m, 2 H), 2.97 (t, 1 H, J = 7.1 Hz, $CHCHCH{=}C$), 3.34−3.42 (m, 4 H, 2 × OCH_2), 4.05−4.12 (m, 1 H, $C{=}CHCHOSi$), 5.34 (ddd, 1 H, J = 1.1, J = 6.6, J = 15.4 Hz, $CH{=}CH$), 5.50 (dd, 1 H, J = 6.6, J = 15.4 Hz, $CH{=}CH$), 7.26 (d, 2 H, J = 8.0 Hz, Ph), 7.77 (d, 2 H, J = 8.2 Hz, Ph), 8.77 (br s, 1 H, NH). ^{13}C NMR (100 MHz, d_8-THF): δ −4.6 (d), −3.7 (d), 14.4 (d), 18.8 (u), 21.4 (d), 22.6 (d), 22.6 (d), 23.4 (u), 25.8 (u), 26.3 (d), 30.4 (u), 32.7 (u), 33.6 (u), 38.7 (d), 39.3 (u), 39.9 (u), 42.1 (u), 47.2 (d), 53.3 (d), 72.1 (u), 72.7 (u), 74.2 (d), 110.6 (u), 128.6 (d), 129.5 (d), 129.7 (d), 135.3 (d), 138.3 (u), 143.2 (u), 166.6 (u). IR (KBr): ν 3431 (m, br), 3222 (m), 2932 (s), 2858 (s), 1654 (m), 1601 (m), 1544 (w), 1497 (w), 1470 (m), 1400 (m), 1341 (m), 1289 (w), 1254 (m), 1217 (w), 1168 (s), 1115 (s), 1039 (w), 1007 (w), 968 (m), 926 (m), 874 (w) 836 (s), 813 (m). MS (EI, 70 eV) *m*/*z* (relative intensity, %): 575 (M^+ − *t*-Bu, 17), 477 (M^+ − Ts, 7), 429 (36), 346 (16), 345 (58), 262 (18), 261 (100), 260 (13), 259 (56), 231 (12), 215 (24), 213 (25), 149 (40), 91 (18). HRMS calcd for $C_{34}H_{56}N_2O_5SiSNa^+$: 655.3577, found 655.3576. **19**: colorless oil; R_f 0.90 (hexanes/EtOAc, 2:1), $[\alpha]_D$ −16.2 (*c* 1.4, $CHCl_3$) [lit. $[\alpha]^{23}_D$ −12.0 (*c* 1.0, $CHCl_3$)].[27a] ^{1}H and ^{13}C NMR spectra of **19** matched those reported previously.[27b]

Method B. BuLi (0.96 mL, 1.6 M in hexanes, 1.54 mmol) was added to a solution of iodide **18** (98% ee, 578 mg, 1.57 mmol) in THF (3 mL) at −78 °C. After the mixture was stirred for 1 h at −78 °C, a cold solution of CuCN (298 mg, 3.33 mmol) and LiCl (283 mg, 6.66 mmol) in THF (4 mL) was added at −78 °C via cannula. The resulting yellow solution was stirred at −78 °C for 30 min. Then a cold solution (−78 °C) of azoalkene **9** (96% ee, 500 mg, 1.28 mmol) in THF (4 mL) was added via cannula, followed by stirring at −78 °C for 30 min. Then Bu_3SnCl (500 mg, 1.54 mmol) was added, followed by stirring at −78 °C for 15 min. Subsequently water (3 mL) was added and the mixture was warmed to room temperature. Then the mixture was diluted with Et_2O (100 mL) and washed with a mixture of saturated aqueous NH_4Cl and concentrated aqueous NH_3 (10:1, 3 × 20 mL). The combined aqueous phases were extracted with Et_2O (3 × 20 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification by chromatography (hexanes/Et_2O, 2:1) gave hydrazone **8** (577 mg, 71%) and stannane **19** (243 mg, 29%).

(−)-(3a′*S*,4′*R*,5′*R*,6a′*R*)-4′-((*S*,*E*)-3-(*tert*-Butyldimethylsilyloxy)oct-1-enyl)-5,5-dimethyl-hexahydro-1′*H*-spiro[[1,3]dioxane-2,2′-pentalen]-5′-ol (22). A solution of hydrazone **8** (300 mg, 0.47 mmol) and cyclohexene (0.96 mL, 9.48 mmol) in THF (15 mL) was treated with $(PhSeO)_2O$ (179 mg, 0.50 mmol) at room temperature, whereby a gas evolution occurred. The mixture was stirred at room temperature for 1 h, and then saturated aqueous $NaHCO_3$ (2 mL) was added. The mixture was extracted with hexanes (2 × 20 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The crude ketone **21** [HRMS (ESI, TOF) calcd for $C_{27}H_{48}O_4SiNa^+$: 487.3220, found 487.3212] was dissolved in EtOH (30 mL), and the solution was treated with $NaBH_4$ (72 mg, 1.90 mmol) at −40 °C. After the mixture was stirred at −40 °C for 7 h, saturated aqueous NH_4Cl (3 mL) was added, and the mixture was warmed to room temperature and extracted with Et_2O (3 × 30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification by chromatography (hexanes/EtOAc, 8:1) gave alcohol **22** (134 mg, 61%) as a colorless oil. R_f 0.54 (hexanes/EtOAc, 2:1), $[\alpha]_D$ −2.5 (*c* 1.1, THF). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.03 (s, 3 H, $SiCH_3$), 0.05 (s, 3 H, $SiCH_3$), 0.85−0.92 (m, 12 H, $SiC(CH_3)_3$, CH_2CH_3), 0.96 (s, 6 H, $C(CH_3)_2$), 1.20−1.58 (m, 9 H), 1.74−1.87 (m, 2 H), 2.02−2.32 (m, 5 H), 2.37−2.52 (m, 1 H), 3.44−3.52 (m, 4 H, 2 × OCH_2), 3.74 (dt, 1 H, J = 6.4, J = 9.2 Hz, $CHOH$), 4.02−4.11 (m, 1 H, CHOSi), 5.43 (dd, 1 H, J = 7.2, J = 15.3 Hz, $CH{=}CH$), 5.54 (dd, 1 H, J = 5.9, J = 15.3 Hz, $CH{=}CH$). ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.7 (d), −4.1 (d), 14.1 (d), 18.3 (u), 22.6 (d), 22.7 (u), 25.2 (u), 26.0 (d), 30.1 (u), 31.8 (u), 35.6 (d), 38.3 (u), 38.5 (u), 40.6 (u), 43.8 (d), 57.8 (d), 72.1 (u), 72.1 (u), 73.4 (d), 78.2 (d), 110.3 (u), 130.7 (d), 135.8 (d). IR (neat): ν 3424 (m, br), 2932 (s), 2858 (s), 1467 (m), 1393 (w), 1360 (w), 1328 (m), 1253 (m), 1219 (m), 1180 (w), 1114 (s), 1009 (m), 970 (m), 870 (m), 836 (s). MS (EI, 70 eV) *m*/*z* (relative intensity, %): 448 (12), 410 (24), 409 (M^+ − *t*-Bu, 100), 378 (25), 377 (84), 334 (20), 324 (23), 323 (90), 317 (30), 305 (13), 291 (11), 263 (14), 251 (15), 232 (12), 231 (58), 230 (12), 223 (21), 213 (16), 209 (19), 203 (15), 187 (22), 188 (11), 175 (30), 173 (11), 161 (37), 159 (15), 149 (24), 147 (15), 135 (16), 133 (23), 131 (19), 129 (10), 128 (27), 119 (13), 117 (22), 107 (11), 105 (22), 99 (17), 95 (17), 93 (15), 91 (17), 83 (14), 81 (16). Anal. Calcd for $C_{27}H_{50}O_4Si$: C, 69.48; H, 10.80. Found: C, 69.32; H, 11.19.

Preparation of Alcohol 22 from Azoalkene 9 without Isolation of Hydrazone 8 and Ketone 21. BuLi (0.96 mL, 1.6 M in hexanes, 1.54 mmol) was added to a solution of iodide **18** (98% ee, 578 mg, 1.57 mmol) in THF (3 mL) at −78 °C. After the mixture was stirred for 1 h at −78 °C, a cold solution (−78 °C) of CuCN (298 mg, 3.33 mmol) and LiCl (283 mg, 6.66 mmol) in THF (4 mL) was added at −78 °C via cannula. The resulting yellow solution was stirred at −78 °C for 30 min. Then a cold solution (−78 °C) of azoalkene **9** (96% ee, 500 mg, 1.28 mmol) in THF (4 mL) was added via cannula, followed by stirring at −78 °C for 30 min. Bu_3SnCl (500 mg, 1.54 mmol) was added, followed by stirring at −78 °C for 15 min. Then water (3 mL) was added, and the mixture was warmed to room temperature. The mixture was diluted with Et_2O (100 mL) and washed with a mixture of saturated aqueous NH_4Cl and concentrated aqueous NH_3 (10:1, 3 × 20 mL). The combined aqueous phases were extracted with Et_2O (3 × 20 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The residue was dissolved in THF (20 mL), cyclohexene (2.60 mL, 25.61 mmol) was added, and the solution was treated with $(PhSeO)_2O$ (461 mg, 1.28 mmol) at room temperature, whereby a gas evolution occurred. Then the mixture was stirred at room temperature for 40 min and cooled to 0 °C, and EtOH (30 mL) was added. Subsequently $NaBH_4$ (291 mg, 7.68 mmol) was added at 0 °C, followed by stirring at 0 °C for 1 h. Then saturated aqueous NH_4Cl (3 mL) was added, and the mixture was warmed to room temperature. The mixture was concentrated in vacuo, and the residue was dissolved in mixture of Et_2O (100 mL) and water (10 mL). The aqueous phase was extracted with Et_2O (3 × 20 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification by chromatography (hexanes/EtOAc, 8:1) gave alcohol **22** (313 mg, 52%) and stannane **19** (236 mg, 70%).

(3a′*S*,4′*R*,5′*R*,6a′*R*)-4′-((*S*,*E*)-3-(*tert*-Butyldimethylsilyloxy)oct-1-enyl)-5,5-dimethyl-hexahydro-1′*H*-spiro[[1,3]dioxane-2,2′-pentalen]-5′-ol (22) and (3a′*S*,4′*R*,5′*R*,6a′*R*)-4′-((*R*,*E*)-3-(*tert*-Butyldimethylsilyloxy)oct-1-enyl)-5,5-dimethylhexahydro-1′*H*-spiro[[1,3]-dioxane-2,2′-pentalen]-5′-ol (24). BuLi (3.20 mL, 1.6 M in hexanes, 5.12 mmol) was added to a solution of iodide *rac*-**18** (1.924 g, 5.22 mmol) in THF (12 mL) at −78 °C. After the mixture was stirred for 1 h at −78 °C, a cold solution (−78 °C) of CuCN (596 mg, 6.66 mmol) and LiCl (563 mg, 13.32 mmol) in THF (8 mL) was added at −78 °C via cannula. The resulting yellow solution was stirred at −78 °C for 30 min. Then a cold solution (−78 °C) of azoalkene **9** (96% ee, 500 mg, 1.28 mmol) in THF (4 mL) was added via cannula, followed by stirring at −78 °C for 30 min. Bu_3SnCl (1.667 g, 5.12 mmol) was added, followed by stirring at −78 °C for 15 min. Then water (4 mL) was added, and the mixture was warmed to room temperature. Subsequently the mixture was diluted with Et_2O (150 mL) and washed with a mixture of saturated aqueous NH_4Cl and concentrated aqueous NH_3 (10:1, 3 × 15 mL). The combined aqueous phases were extracted with Et_2O (3 × 20 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The residue was dissolved in THF (20 mL), cyclohexene (2.60 mL, 25.61 mmol) was added, and the solution was treated with $(PhSeO)_2O$ (461 mg, 1.28 mmol) at room temperature, whereby a gas evolution occurred. Then the mixture was stirred at room temperature for 40 min and cooled to 0 °C, and EtOH (30 mL) was added. Subsequently $NaBH_4$ (388 mg, 10.24 mmol) was added at 0 °C, followed by stirring at 0 °C for 1 h. Then saturated aqueous NH_4Cl (3 mL) was added, and the mixture was warmed to room temperature. The mixture was concentrated in vacuo, and the residue was dissolved in mixture of Et_2O (100 mL) and water (10 mL). The aqueous phase was extracted with Et_2O (3 × 15 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification by chromatography (hexanes/EtOAc, 8:1) gave a mixture of alcohols **22** and **24** in a ratio of 1:1 (373 mg, 62%) and stannane *rac*-**19** (2.163 g, 92%) as colorless oils. R_f 0.54 (hexanes/EtOAc, 2:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.03 (s, 2 × 3 H, 2 × $SiCH_3$), 0.05 (s, 2 × 3 H, 2 × $SiCH_3$), 0.86−0.91 (m, 2 × 12 H, 2 × $SiC(CH_3)_3$, 2 × CH_2CH_3), 0.95 (s, 3 H, $C(CH_3)_2$, **24**), 0.96 (s, 3 H, $C(CH_3)_2$, **22**), 0.97 (s, 3 H, $C(CH_3)_2$, **22**), 0.98 (s, 3 H, $C(CH_3)_2$, **24**), 1.20−1.58 (m, 2 × 9 H), 1.67−1.89 (m, 2 × 3 H), 2.01−2.30 (m, 2 × 5 H), 2.38−2.51 (m, 2 × 1 H), 3.44−3.51 (m, 2 × 4 H, 4 × OCH_2), 3.72 (dt, 1 H, J = 6.6, J = 9.6 Hz, C*H*OH, **24**), 3.75 (dt, 1 H, J = 6.6, J = 9.6 Hz, C*H*OH, 6), 4.02−4.10 (m, 2 × 1 H, CHOSi), 5.40 (dd, 1 H, J = 8.2, J = 15.4 Hz, C*H*═CH, **24**), 5.43 (dd, 1 H, J = 7.1, J = 15.4 Hz, C*H*═CH, **22**), 5.53 (dd, 1 H, J = 6.6, J = 15.4 Hz, CH═C*H*, **24**), 5.55 (dd, 1 H, J = 6.0, J = 15.4 Hz, CH═C*H*, **22**). ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.7 (d), −4.6 (d), −4.2 (d), −4.1 (d), 14.0 (d), 18.3 (d), 22.5 (d), 22.6 (d), 22.6 (u), 25.1 (u), 25.9 (d), 30.0 (u), 31.7 (u), 35.4 (d), 35.5 (d), 38.0 (u), 38.2 (u), 38.4 (u), 40.5 (u), 40.6 (u), 40.6 (u), 40.7 (u), 43.7 (d), 43.8 (d), 57.7 (d), 57.8 (d), 71.9 (u), 71.9 (u), 72.0 (u), 72.0 (u), 73.2 (d), 73.5 (d), 78.0 (d), 78.1 (d), 110.1 (u), 110.1 (u), 130.4 (d), 130.7 (d), 135.6 (d), 135.8 (d). IR (neat): ν 3409 (m, br), 2953 (s), 2858 (s), 1468 (m), 1393 (w), 1360 (w), 1329 (m), 1253 (m), 1219 (m), 1115 (s), 1009 (m), 970 (m), 870 (m), 836 (s). MS (CI, CH_4) *m*/*z* (relative intensity, %): 467 (18), 465 (12), 451 (M^+ − Me, 25), 450 (15), 449 (37), 410 (21), 409 (M^+ − *t*-Bu, 67), 378 (14), 377 (50), 363 (14), 335 (22), 334 (13), 333 (15), 323 (34), 318 (25), 317 (100), 249 (12), 231 (43), 221 (11), 215 (15).

(−)-(3a*S*,4*R*,5*R*,6a*R*)-5-Hydroxy-4-((*S*,*E*)-3-hydroxyoct-1-enyl)-hexahydropentalen-2(1*H*)-one (23) and (−)-(3a*S*,4*R*,5*R*,6a*R*)-5-Hydroxy-4-((*R*,*E*)-3-hydroxyoct-1-enyl)hexa-hydropentalen-2(1*H*)-one (25). A mixture of acetals **22** and **24** (1.300 g, 2.79 mmol), obtained from azoalkene **9** (96% ee) and iodide *rac*-**18**, was dissolved in acetone (100 mL) and water (10 mL). TsOH (230 mg) was added at room temperature, and the mixture was stirred at room temperature for 16 h. Then saturated aqueous $NaHCO_3$ (8 mL) was added. The mixture was extracted with Et_2O (3 × 80 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification by chromatography (hexanes/EtOAc, 1:3) gave ketodiol **23** (314 mg, 42%) and ketodiol **25** (330 mg, 44%). **23**: colorless oil, R_f 0.40 (hexanes/EtOAc, 1:4), $[\alpha]_D$ −7.9 (*c* 1.4, $CHCl_3$) (lit. $[\alpha]^{23}_D$ −8.2 (*c* 1.53, $CHCl_3$)[18c]). **25**: colorless oil, R_f 0.32 (hexanes/EtOAc, 1:4), $[\alpha]_D$ −23.5 (*c* 1.1, $CHCl_3$) [lit. $[\alpha]^{24}_D$ −23.9 (*c* 1.58, $CHCl_3$)[18c]]. IR, ^{1}H and ^{13}C NMR spectra of **23**[6,18] and **25**[18] matched those reported previously.

(−)-(3a*S*,4*R*,5*R*,6a*R*)-5-Hydroxy-4-((*S*,*E*)-3-hydroxyoct-1-enyl)-hexahydropentalen-2(1*H*)-one (23). Acetal **22** (400 mg, 0.857 mmol), obtained from azoalkene **9** (96% ee) and iodide **18** (98% ee), was dissolved in a mixture of acetone (30 mL) and water (3 mL). TsOH (70 mg) was added at room temperature, and the mixture was stirred at room temperature for 16 h. Then saturated aqueous $NaHCO_3$ (3 mL) was added. The mixture was extracted with Et_2O (3 × 20 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification by chromatography (hexanes/EtOAc, 1:3) gave ketodiol **23** (198 mg, 87%) and ketodiol **25** (4 mg, 2%).

(−)-(3a*S*,4*R*,5*R*,6a*R*)-5-(*tert*-Butyldimethylsilyloxy)-4-((*S*,*E*)-3-(*tert*-butyldimethyl-silyl-oxy)oct-1-enyl)hexahydropentalen-2(1*H*)-one (7). A solution of ketodiol **23** (250 mg, 0.94 mmol) in DMF (25 mL) was treated with imidazole (319 mg, 4.69 mmol) at 0 °C, followed by stirring at 0 °C for 30 min. Then $ClSiMe_2t$-Bu (311 mg, 2.06 mmol) was added at 0 °C. The mixture was stirred at room temperature for 16 h, then diluted with Et_2O (150 mL), washed with water (2 × 10 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by chromatography (hexanes/Et_2O, 10:1) gave ketone **7** (435 mg, 94%) as a colorless oil. $[\alpha]^{22}_D$ −34.4 (*c* 0.5, THF). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.01 (s, 3 H, $SiCH_3$), 0.04 (s, 6 H, 2 × $SiCH_3$), 0.04 (s, 3 H, $SiCH_3$), 0.84−0.92 (m, 21 H, 2 × $SiC(CH_3)_3$, CH_2CH_3), 1.20−1.54 (m, 9 H), 2.12−2.62 (m, 7 H), 2.64−2.80 (m, 1 H), 3.91−4.00 (m, 1 H, C*H*(OSi)-CHCH═C), 4.01−4.09 (m, 1 H, C═CHC*H*OSi), 5.39−5.54 (m, 2 H, C*H*═C*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.7 (d), −4.6 (d), −4.6 (d), −4.2 (d), 14.1 (d), 18.1 (u), 18.3 (u), 22.7 (u), 25.1 (u), 25.9 (d), 25.9 (d), 31.9 (u), 35.7 (d), 38.6 (u), 42.4 (u), 43.1 (d),

43.2 (u), 46.1 (u), 57.6 (d), 73.1 (d), 79.3 (d), 129.7 (d), 135.2 (d), 220.2 (u). IR ($CHCl_3$): ν 2931 (s), 2857 (s), 1742 (s), 1467 (m), 1406 (m), 1385 (m), 1363 (m), 1254 (s), 1121 (s), 1081(m), 1004 (m), 971 (m), 940 (w), 897 (m), 837 (s). MS (EI, 70 eV) *m*/*z* (relative intensity, %): 479 (M^+ − Me, 1.5), 439 (14), 438 (40), 437 (M^+ − *t*-Bu, 100), 327 (12), 305 (16), 291 (12), 189 (12), 171 (10), 149 (13), 147 (61), 117 (12). HRMS calcd for $C_{28}H_{54}O_3Si_2-C_4H_9$: 437.290728, found 437.290783.

(+)-(*E*)- and (−)-(*Z*)-((1*S*,2*R*)-2-(2-Phenylpropan-2-yl)cyclohexyl) 2-((3a*S*,4*R*,5*R*,6a*S*)-5-(*tert*-Butyldime-thylsilyloxy)-4-((*S*,*E*)-3-(*tert*-butyldimethylsilyloxy)oct-1-enyl)hexahydro-pentalen-2(1*H*)-ylidene)acetate (*E*-27 and *Z*-27). BuLi (0.76 mL, 1.6 M in hexanes, 1.33 mmol) was added to a solution of (1*S*,2*R*)-2-(2-phenylpropan-2yl)cyclohexyl 2-(dimethoxyphosphoryl)acetate (491 mg, 1.33 mmol) in THF (2 mL) at −78 °C. The solution of the lithium salt **26** was warmed to room temperature for 15 min and then cooled to −62 °C. Then a solution of ketone **7** (150 mg, 0.30 mmol) in THF (0.8 mL) was added within 10 min. The mixture was stirred at −62 °C for 5 days. Then saturated aqueous NH_4Cl (10 mL) was added, and the mixture was warmed to room temperature. The aqueous phase was separated and diluted with water until a clear solution was formed. The aqueous phase was extracted with Et_2O (3 × 20 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification by chromatography (hexanes/Et_2O, 20:1, then 10:1) afforded a mixture of esters *E*-**27** and *Z*-**27** (197 mg, 88%) (R_f 0.62 (hexanes/EtOAc, 10:1)) in a ratio 95:5 (^{1}H NMR: δ (C=CHCO) 5.11 (*E*-**27**); δ (C=CHCO) 5.16 (*Z*-**27**)) as a colorless oil. HPLC (Kromasil-Si-100, 250 × 30 mm, hexanes/EtOAc, 98:2, UV: 254 nm) gave ester *E*-**27** (181 mg, 81%) of ≥99% de as a colorless oil. *E*-**27**: $[\alpha]_D$ +9.7 (*c* 1.5, THF). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.03 (s, 3 H, $SiCH_3$), 0.04 (s, 6 H, 2 × $SiCH_3$), 0.06 (s, 3 H, $SiCH_3$), 0.85−0.91 (m, 21 H, 2 × $SiC(CH_3)_3$, CH_2CH_3), 1.00−1.54 (m, 14 H), 1.23 (s, 3 H, $CHCH_3$), 1.33 (s, 3 H, $CHCH_3$), 1.63−1.73 (m, 3 H), 1.87−2.32 (m, 6 H), 2.41−2.52 (m, 2 H), 2.70−2.87 (m, 2 H), 3.77−3.85 (m, 1 H, C*H*(OSi)CHCH=C), 4.05−4.11 (m, 1 H, C=CHC*H*OSi), 4.73−4.81 (m, 1 H, CHOCO), 5.10−5.12 (m, 1 H, C=CHCO), 5.43−5.54 (m, 2 H, C*H*=C*H*), 7.07−7.29 (m, 5 H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.5 (d), −4.4 (d), −4.3 (d), −3.9 (d), 14.3 (d), 18.3 (u), 18.4 (u), 22.8 (u), 25.0 (u), 25.3 (u), 25.5 (d), 26.1 (d), 26.1 (d), 26.2 (u), 27.3 (u), 27.8 (d), 32.0 (u), 33.8 (u), 38.8 (u), 38.9 (d), 39.6 (u), 40.0 (u), 40.1 (u), 42.6 (u), 44.6 (d), 51.3 (d), 56.1 (d), 73.3 (d), 73.8 (d), 78.9 (d), 113.3 (d), 124.8 (d), 125.5 (d), 127.9 (d), 130.4 (d), 134.7 (d), 151.6 (u), 165.7 (u), 166.7 (u). IR (neat): ν 2931 (s), 2858 (s), 1708 (s), 1659 (m), 1600 (w), 1496 (w), 1467 (m), 1368 (m), 1253 (s), 1214 (s), 1125 (s), 1031 (m), 1006 (w), 968 (m), 910 (m), 838 (s). MS (CI, isobutane) *m*/*z* (relative intensity, %): 737 (1.4), 736 (1.2), 735 (1.1), 679 (M^+ − *t*-Bu, 9), 607 (14), 606 (46), 605 (95), 479 (18), 406 (28), 405 (100), 273 (12), 201 (37), 119 (19). Anal. Calcd for $C_{45}H_{76}O_4Si_2$: C, 73.31; H, 10.39. Found: C, 73.30; H, 10.02. *Z*-**27**: colorless oil, $[\alpha]_D$ −39.8 (*c* 1.7, THF). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.01 (s, 3 H, $SiCH_3$), 0.02 (s, 3 H, $SiCH_3$), 0.03 (s, 3 H, $SiCH_3$), 0.05 (s, 3 H, $SiCH_3$), 0.81−0.92 (m, 21 H, 2×$C(CH_3)_3$, CH_2CH_3), 0.92−1.72 (m, 17 H), 1.23 (s, 3 H, $CHCH_3$), 1.32 (s, 3 H, $CHCH_3$), 1.90−2.46 (m, 7 H), 2.56−2.89 (m, 3 H), 3.82 (dt, 1 H, *J* = 6.9, *J* = 8.2 Hz, C*H*(OSi)CHCH=C), 4.02−4.10 (m, 1 H, C=CHC*H*OSi), 4.73−4.83 (m, 1 H, C*H*OCO), 5.16−5.18 (m, 1 H, C=CHCO), 5.39−5.52 (m, 2 H, C*H*=C*H*), 7.07−7.29 (m, 5 H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.7 (d), −4.5 (d), −4.5 (d), −4.1 (d), 14.1 (d), 18.2 (u), 18.3 (u), 22.7 (u), 24.8 (u), 25.2 (u), 25.9 (d), 26.0 (d), 26.1 (u), 26.4 (d), 26.7 (d), 27.3 (u), 31.9 (u), 33.7 (u), 36.1 (u), 37.2 (d), 38.7 (u), 40.1 (u), 41.7 (u), 43.3 (u), 46.8 (d), 51.3 (d), 57.1 (d), 73.0 (d), 73.8 (d), 79.0 (d), 113.2 (d), 124.9 (d), 125.6 (d), 127.9 (d), 130.4 (d), 134.6 (d), 151.6 (u), 165.8 (u), 167.0 (u). IR (KBr): ν 2933 (s), 2858 (s), 1703 (s), 1656 (m), 1600 (w), 1497 (w), 1466 (m), 1366 (m), 1325 (w), 1253 (m), 1208 (s), 1126 (s), 1037 (m), 1005 (w), 967 (m), 937 (w), 904 (m), 838 (s). MS (EI, 70 eV) *m*/*z* (relative intensity, %): 679 (M^+ − *t*-Bu, 3), 481 (14), 480 (39), 479 (100), 404 (11), 347 (26), 329 (20), 273 (16), 119 (81), 105 (65), 91 (15). MS (CI, CH_4) *m*/*z* (relative intensity, %): 737 (6), 736 (10), 735 (17), 722 (16), 721 (33), 681 (10), 680 (28), 679 (59), 607 (12), 606 (39), 605 (83), 521 (35), 481 (14), 480 (37), 479 (100), 474 (16), 473 (57), 433 (19), 406 (25), 405 (99), 389 (16), 387 (27), 347 (23), 310 (17), 301 (11), 283 (15), 282 (95), 280 (29), 273 (63), 201 (61), 199 (11), 123 (20), 119 (40), 105 (18). HRMS calcd for $C_{45}H_{76}O_4Si_2-C_{19}H_{29}$: 479.301293, found 479.301165.

(*E*)-2-((3a*S*,4*R*,5*R*,6a*S*)-5-(*tert*-Butyldimethylsilyloxy)-4-((*S*,*E*)-3-(*tert*-butyldimethyl-silyloxy)oct-1-enyl)hexahydropentalen-2(1*H*)-ylidene)ethanol (6). (*i*-Bu)$_2$AlH (0.57 mL, 1 M in THF) was added to a solution of ester *E*-**27** (140 mg, 0.19 mmol) in THF (4 mL) at 0 °C. The mixture was warmed to ambient temperature and stirred for 2 h. Then aqueous NH_4Cl (5 mL) was added at 0 °C. Water (50 mL) was added, and the mixture was extracted with CH_2Cl_2 (5 × 30 mL) and Et_2O (5 × 30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification by chromatography (hexanes/EtOAc, 10:1) afforded alcohol **6** (87 mg, 88%) as a colorless oil. R_f 0.13 (hexanes/EtOAc, 10:1), $[\alpha]_D$ +17.1 (*c* 0.43, THF). ^{1}H NMR (300 MHz, C_6D_6): δ 0.09 (s, 3 H, $SiCH_3$), 0.12 (s, 3 H, $SiCH_3$), 0.15 (s, 3 H, $SiCH_3$), 0.15 (s, 3 H, $SiCH_3$), 0.80 (bs, 1 H, OH), 0.92 (t, 3 H, *J* = 6.7 Hz, CH_2CH_3), 0.99 (s, 9 H, $SiC(CH_3)_3$), 1.06 (s, 9 H, $SiC(CH_3)_3$), 1.23−1.74 (m, 9 H), 1.94−2.42 (m, 8 H), 3.73 (dt, *J* = 6.7, *J* = 8.9 Hz, 1 H, =CHCHC*H*OSi), 3.96 (d, 2 H, *J* = 6.7 Hz, CH_2OH), 4.10−4.17 (m, 1 H, =CHC*H*OSi), 5.45−5.53 (m, 1 H, =C*H*CH_2OH), 5.53−5.67 (m, 2 H, C*H*=C*H*). ^{13}C NMR (75 MHz, C_6D_6): δ −4.9 (d), −4.7 (d), −4.6 (d), −4.2 (d), 13.9 (d), 18.0 (u), 18.1 (u), 22.7 (u), 25.3 (u), 25.8 (d), 25.8 (d), 31.9 (u), 35.8 (u), 37.9 (d), 38.2 (u), 38.8 (u), 42.5 (u), 44.7 (d), 56.3 (d), 60.2 (u), 73.1 (d), 78.4 (d), 121.8 (d), 130.9 (d), 134.6 (d), 144.5 (u). IR ($CHCl_3$): ν 3362 (m, br), 2932 (s), 2858 (s), 1677 (w), 1466 (m), 1363 (m), 1253 (s), 1114 (s), 1005 (m), 971 (m), 910 (w), 838 (s). MS (EI, 70 eV) *m*/*z* (relative intensity, %): 507 (1), 466 (13), 465 (31), 451 (20), 449 (14), 448 (30), 447 (77), 390 (25), 374 (28), 373 (100), 334 (11), 333 (40), 319 (10), 242 (14), 241 (75), 215 (13), 171 (27), 157 (11), 149 (22), 147 (24), 145 (33), 143 (17), 129 (11), 117 (12), 105 (19), 93 (12), 91 (11). MS (CI, CH_4) *m*/*z* (relative intensity, %): 524 (0.5), 523 (1.7), 522 (2.6), 521 (6.6), 507 (14), 465 (17), 391 (30), 389 (12), 375 (12), 374 (28), 373 (100), 241 (16). HRMS calcd for $C_{30}H_{58}O_3Si_2-C_4H_9$: 465.322028, found 465.321982.

***tert*-Butyl 2-((*E*)-2-((3a*S*,4*R*,5*R*,6a*S*)-5-Hydroxy-4-((*S*,*E*)-3-hydroxyoct-1-enyl)hexa-hydro-pentalen-2(1*H*)-ylidene)ethoxy)-acetate (28).** A solution of alcohol **6** (73 mg, 0.14 mmol) and Bu_4NHSO_4 (47 mg, 0.14 mmol) in CH_2Cl_2 (3 mL) was treated with aqueous 50% NaOH (2.5 mL) and $BrCH_2COOt$-Bu (82 mg, 0.42 mmol). The mixture was stirred for 3 h. Then a further portion of $BrCH_2COOt$-Bu (82 mg, 0.42 mmol) was added. After the reaction mixture was stirred for 2 h, ice (5 g) was added. The mixture was extracted with CH_2Cl_2 (4 × 20 mL), and the organic phases were dried ($MgSO_4$) and concentrated. The residue was dried in high vacuo and dissolved in THF (3 mL), and NBu_4F (1.0 solution in THF, 0.84 mL, 0.84 mmol) was added. The mixture was stirred for 16 h at ambient temperature. Then the mixture was diluted with Et_2O (10 mL) and washed with saturated aqueous NaCl (40 mL). The aqueous phase was extracted with Et_2O (4 × 20 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification by chromatography (hexanes/EtOAc, 5:2) afforded ester **28** (51 mg, 89%) as a colorless oil. R_f 0.42 (hexanes/EtOAc, 1:4), $[\alpha]_D$ +64.8 (*c* 0.73, THF) [lit. $[\alpha]^{22}_D$ +65.6 (*c* 10.5, THF)[5b,6]]. ^{1}H and ^{13}C NMR spectra were identical with those of **28** reported previously.[5b,6]

(2-((*E*)-2-((3a*S*,4*R*,5*R*,6a*S*)-5-Hydroxy-4-((*S*,*E*)-3-hydroxyoct-1-enyl) hexahydro-pentalen-2(1*H*)-ylidene)ethoxy)acetic acid) (3). A solution of ester **28** (41 mg, 0.10 mmol) in MeOH (2 mL) was treated with aqueous NaOH (1.0 M, 0.6 mL). The mixture was stirred for 4 h at ambient temperature, and then saturated aqueous NH_4Cl (2.5 mL) and water (2.5 mL) were added. The pH

value of the solution was adjusted to 4−5 by the portion-wise addition of solid NaH_2PO_4. The mixture was extracted with EtOAc (5 × 15 mL), and the combined organic phases were dried ($MgSO_4$). Concentration in vacuo gave acid **3** (32 mg, 90%) as a colorless oil. R_f 0.24 (CH_2Cl_2/MeOH, 4:1). ^1H and ^{13}C NMR spectra of **3** matched those reported previously.[5b,6]

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Supporting Information Available: Copies of the NMR spectra of **3**, **6**−**8**, **19**, **23**−**25**, *E*-**27**, *Z*-**27**, and **28**. This material is available free of charge via the Internet at http://pubs.acs.org.

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