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A New Strategy for the Enantioselective Synthesis of Carba-Prostacyclin Analogues Based on Organocopper Conjugate Addition to a Bicyclic Azoene and Its Application to the Synthesis of 13,14-Dinor-*inter-p*-phenylene Carbacyclin

Marc van Bergen and Hans-Joachim Gais*

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

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Abstract: An enantioselective synthesis of *E*/*Z*-13,14-dinor-*inter-p*-phenylene carbacyclin (*E*/*Z*-**2d**) by a new strategy has been realized that holds the prospect of serving as a general route for carba-prostacyclin analogues. The key intermediate in this synthesis is the bicyclic azoene Ts-**9,** and the key step is the regio- and stereoselective conjugate addition of the chiral arylcopper compound Cu-**8d**/P-*n*-Bu_3 to the azoene with formation of hydrazone **7d**. Enantioselective synthesis of azoene Ts-**9** of 95% ee from ketone **4** was accomplished in four and five steps, respectively. Thus, enantioselective deprotonation of bicyclic ketone **4** with chiral base Li-**10** and trapping of lithium enolate **11** with $ClSiMe_3$ gave enol ether **12**, which was chlorinated with *N*-chlorosuccinimide (NCS) to afford chloro ketone **13**. Alternatively, chloro ketone **13** was also prepared upon chlorination of **11** with NCS. Chloro ketone **13** was converted to chloro hydrazone **14**, which upon treatment with a mild base furnished azoene Ts-**9**. Arylcopper compound **8d** of 98% ee was obtained in two steps from alcohol **16**, which was prepared by enantioselective reduction of ketone **17** with (−)-diisopinocampheylchloroborane. Carbacyclin derivative *E*/*Z*-**2d** was found to be essentially inactive as an inhibitor of ADP induced human platelet aggregation, having an IC_{50} of >10 μmol/L.

Background and Retrosynthetic Analysis

Ever since its discovery in 1976 by Vane et al.,[1] prostacyclin (**1**) (Scheme 1) has attracted the attention of chemistry, medicine, and biology.[2−6] It is the most potent endogenous inhibitor of blood platelet aggregation and a strong vasodilator. Prostacyclin plays together with nitric oxide an important inhibitory role in the local control of vascular tone and platelet aggregation.[7,8] Both compounds are produced in the vascular endothelium, which seems to be of considerable importance in coronary artery disease.[9] The characteristic modes of action of prostacyclin are mediated through specific receptors, which are distributed not only in the cardiovascular system and peripheral organs but also in the central nervous system.[10−16] The latter and most recent observation strongly suggests that prostacyclin not only acts as an important regulator of haemostasis but also plays a significant role in neuronal activity. Because of the inherent chemical and metabolic instability of prostacyclin, which is mainly due to the ring O-atom and the enzymatic degradation of both the α- and ω-side chain, intensive efforts have been made to find stable and potent analogues in a quest for drug candidates.[3,5,6] These efforts were awarded by the finding of the carba-prostacyclin analogues carbacyclin (**2a**)[17] and isocarbacyclin (**3a**).[18] Although carbacyclin and isocarbacyclin are chemically stable and biologically active prostacyclin mimics, both show a reduced activity as compared to prostacyclin. Modification of the ω-side chain of **2a** and **3a** proved to be the key for the attainment of highly active analogues.[3,5,6] For example iloprost (**2b**)[19] and the 15-deoxy tolyl isocarbacyclin derivative **3c**[15] have significantly higher activities than **1**. Iloprost has already been marketed for the treatment of peripheral vascular decease, as for example

* To whom correspondence should be addressed. E-mail: Gais@RWTH-Aachen.de.

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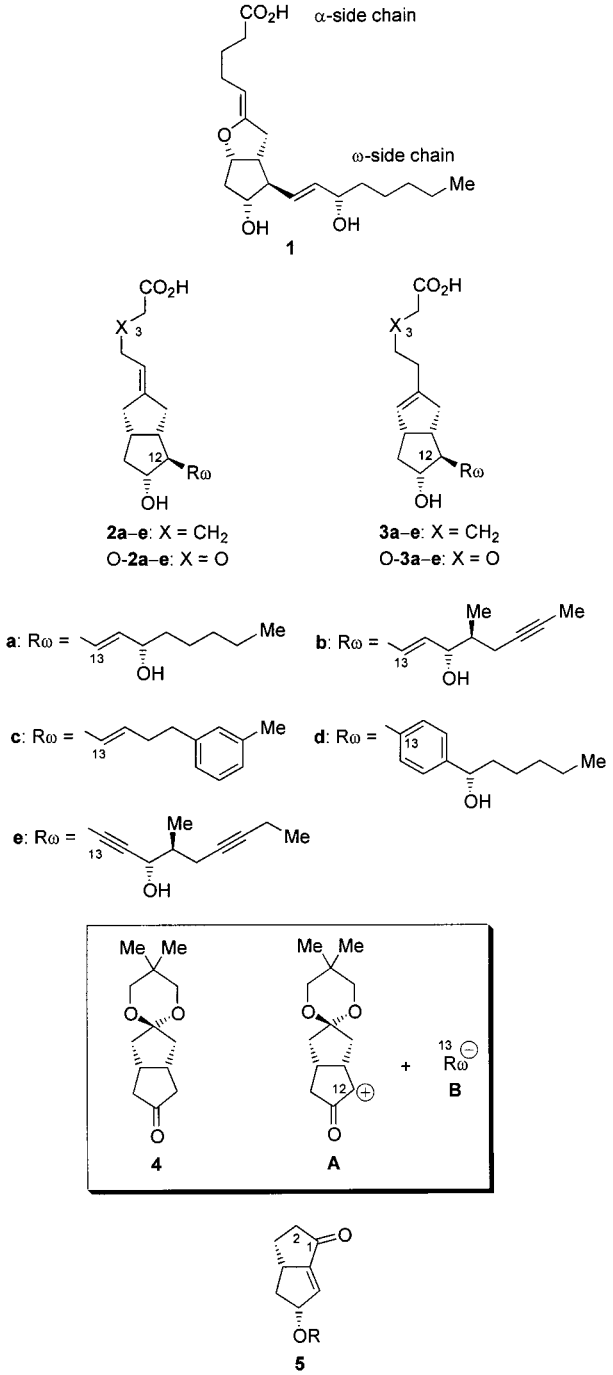
Scheme 1. Prostacyclin and Carba-Prostacyclin Analogues.



advanced thrombangiitis obliterans,[4,20] and the isocarbacyclin derivative is not only a neuronal apoptosis inhibitor but also an excellent probe for a study of the prostacyclin receptors in the brain.[15] While modification of the ω-side chain conveyed high biological activities to the analogues,[3,5,6] introduction of an O-atom in the 3-position of the α-side chain as in O-**2a**,[21] O-**2e**,[22,23] O-**3a**,[21,24,25] and O-**3b**[24] provided for a significantly higher metabolic stability,[22] because of inhibition of β-oxidation. Both the 3-oxa carbacyclin derivative cicaprost (O-**2e**)[26−29] and the 3-oxa isocarbacyclin derivative O-**3b**[24] are not only highly active and metabolically stable but, most importantly, also orally active. In addition to being a potent analogue of prostacyclin cicaprost was recently shown to have a high potency for the reduction of lung metastasis of mammary carcinomas in rats.[26]

Currently there is much interest in devising new general routes to carbacyclins and isocarbacyclins[30] as well as in the development of new carba-prostacyclin analogues as drug candidates and in particular for receptor studies.[15,31] One of the most attractive building blocks for the synthesis of carba-prostacyclins is the bicyclic ketone **4**,[32] which is also being used as starting material in the large scale synthesis of iloprost.[33] First, ketone **4** possesses the complete *cis*-bicyclo[3.3.0]octane skeleton of the target molecules and carries functional groups in positions appropriate for the step-by-step attachment of the side chains. Second, its concave−convex structure allows for a stereoselective functionalization.[3,5,6] Third, ketone **4** is readily available from the corresponding diketone,[32] which can be prepared on large scale by Weiss reaction[34] or obtained from commercial sources. Known enantioselective syntheses of carbacyclins and isocarbacyclins starting from **4** feature with only one exception[21] a stepwise construction of the ω-side chain through olefination of a protected β-hydroxy aldehyde, derived from the bicyclic ketone through introduction of an aldehyde group in α-position of the carbonyl group.[3,5,6] Although some of these syntheses are quite efficient, it would be highly interesting to have an alternative strategy for the enantioselective synthesis of carba-prostacyclin analogues, which allows for the establishment of all kinds of complete ω-side chains (C13−Cω) in a single step through addition of a nucleophilic side chain building block corresponding to synthon **B** to an electrophilic bicyclic building block corresponding to synthon **A** with formation of the C12−C13 bond.[35] If such a strategy could be successfully implemented, it would permit access not only to **2a**−**e**, **3a**−**e**, and their 3-oxa derivatives but also to analogues, which are hitherto

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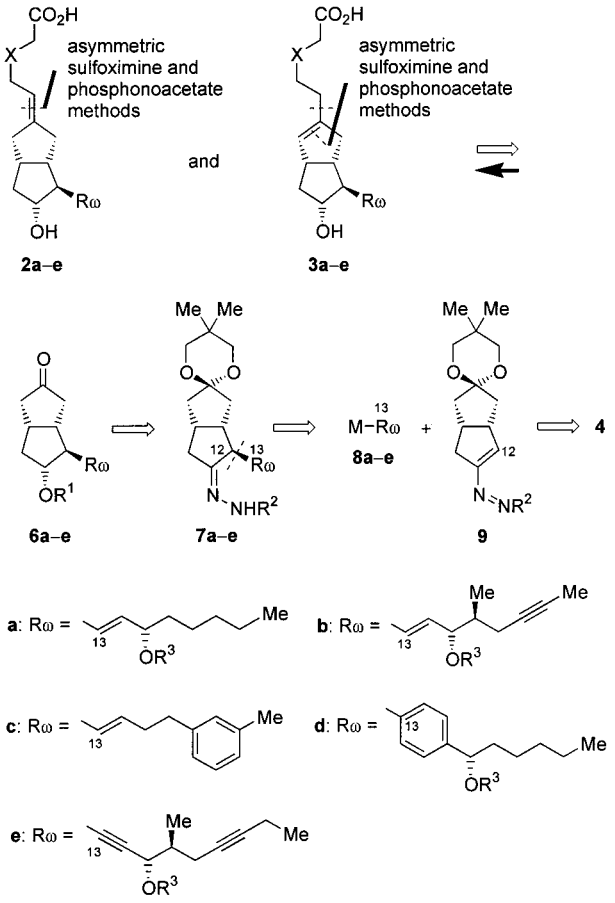
Scheme 2. Azoene Strategy for Carba-Prostacyclin Analogues



not directly accessible from **4**, as for example the *inter*-phenylene analogues **2d** and **3d** and their 2-oxa derivatives. Ikegami and Shibasaki had reported elegant syntheses of *rac*-**2a** and *rac*-**3a**,[36−38] which feature as key step a conjugate addition of a nucleophilic side chain building block to the bicyclic enone *rac*-**5**.[39]Although enone **5** should allow for the addition of all kinds of nucleophilic *ω*-side chain building blocks, several correction steps are necessary for the 1,2-transposition of the carbonyl group of the addition product to allow for its conversion either to a carbacyclin or an isocarbacyclin[36−38,30e] and synthesis of enantiomerically pure **5** from 1,3-cyclooctadiene requires a multistep sequence including kinetic resolution.[40−42] We envisaged as key step and as key building blocks of a new strategy for the enantioselective synthesis of both carbacyclins **2a**−**e** and isocarbacyclins **3a**−**e** a conjugate addition of the organometallic side chain building blocks **8a**−**e** to the bicyclic azoene **9** with stereoselective formation of the C12−C13 bond (Scheme 2). While enantioselective synthesis of **9** and **8b**−**d** would still have to be developed, those of Cu-**8a**[43] and of a potential precursor of **8e**[30d] have already been accomplished. The feasibility of a conjugate addition of the arylcopper derivative Cu-**8d** to **9** was indicated by a communication of Sacks and Fuchs in 1975,[44a] in which they described a new method for the α-phenylation of ketones, which encompasses as key step a conjugate addition of PhCu or Ph_2CuLi to the corresponding *N*-tolylsulfonyl (Ts) azoenes. Although conjugate addition of (1-alkenyl)copper reagents to azoenes has not been reported,[45] it is to be expected that they react in a manner similar to that of the phenylcopper reagents. Thus, prospects for the realization of an addition of Cu-**8a**−**c** to **9** should be good. Whether alkynylmetal compound **8e** will also be capable to undergo a conjugate addition to azoene **9** is more difficult to predict at present, since addition of acetylides to azoenes has not been described.[45] However, it is in principle possible to fine-tune the reactivity of **8** and **9** through variation of the metal atom and of the substituent R at the N-atom. For example, it has been shown that conjugate addition to azoenes is not restricted to organocopper reagents and the *N*-Ts derivatives but also proceeds in the case of the *N*-aryl derivatives and Grignard reagents.[46,47] Key intermediates of the route depicted in Scheme 2 are the bicyclic ketones **6a**−**e** lacking the α-side chain. Their highly stereoselective and regioselective conversion to both the carbacyclins **2a**−**e** and isocarbacyclins **3a**−**e**, including their important 3-oxa analogues, by the asymmetric sulfoximine methods[30g,48−50] and the asymmetric phosphonoacetate method,[21,30b,30c,51,52] developed in our and other laboratories by using achiral ketone **4** as model compound, has either already been accomplished or can be envisioned. The new *inter*-phenylene carbacyclin **2d** was chosen as a probe for the feasibility of the strategy depicted in Scheme 2 because of the following reasons. Incorporation of phenylene groups into the α-side chain of carbacyclin (**2a**) gave highly active and metabolically stable agonists of prostacyclin.[53] It was, thus, of interest to see which effect the introduction of a *p*-phenylene group at C13,C14 of **2a** would have upon its biological activities. A structural modification of this type carried out in the case of 11-deoxyprostaglandin E_1 resulted in analogue AH13205, which turned out to be a highly selective prostanoid EP_2 receptor agonist.[54] A further stimulus for the choice of **2d** as target molecule came from the fact that no direct methods for its

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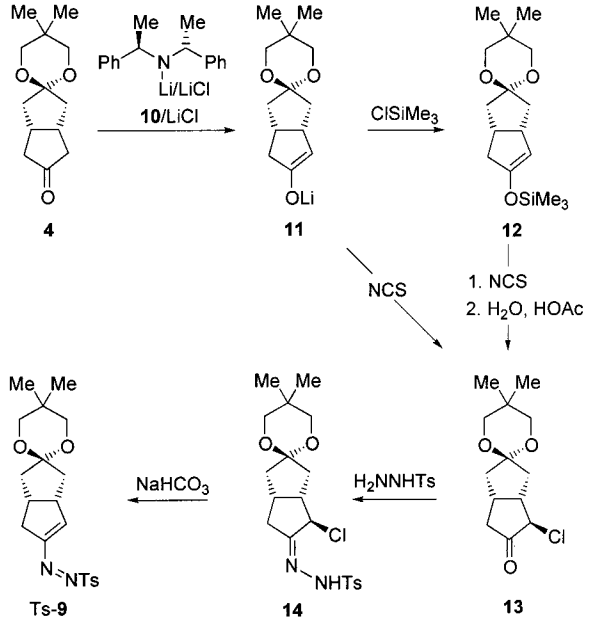
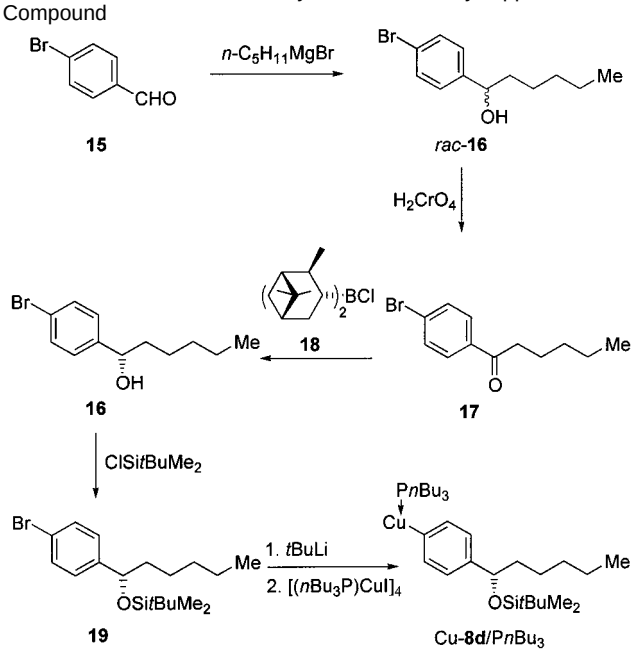
Scheme 3. Enantioselective Synthesis of the Azoene



Scheme 4. Enantioselective Synthesis of the Arylcopper Compound



synthesis from ketone **4** are available.[55] Synthesis of **2d** according to Scheme 2 demands a conjugate addition of the chiral organocopper compound Cu-**8d** to the chiral azoene **9**. This should be accomplished by using the two building blocks in a molar ratio not being much different from 1:1 because of economical reasons. Precedent from Noyori's three-component coupling synthesis of prostaglandins[56] suggested that this goal might be achievable by using a tributylphosphine complex of Cu-**8d**.

Results and Discussion

Enantioselective Synthesis of the Azoene. The *N*-Ts azoene Ts-**9** was selected because of the many methods available for the cleavage of *N*-Ts hydrazones with formation of the parent ketones.[44b,57] The sequence leading from ketone **4** to azoene Ts-**9**, which utilizes as a key step the facile 1,4-elimination of chlorohydrazones,[45] is shown in Scheme 3. Enantioselective deprotonation of ketone **4** with lithium amide Li-**10** in the presence of 1 equiv of LiCl[58] at −100 °C in THF and trapping of the intermediate lithium enolate **11** with $ClSiMe_3$ gave after a chromatographic purification enol ether **12** of 90% ee in 80% yield.[30b,f,g,59] Because of the ready hydrolysis of **12** on silica gel, chromatography has to be carried out as rapidly as possible. The chiral amine H-**10** could be recovered in 70% yield. Synthesis of chloroketone **13** was achieved by chlorination of enol ether **12** with *N*-chlorosuccinimide (NCS).[60,61] Thus, reaction of **12**, which should be free of amine H-**10**, with NCS at room temperature in methylene chloride followed by a hydrolysis of the putative chlorinated enol ether and the NCS adduct,[62] whose formation was indicated by thin-layer chromatography (chlorination of **12** and hydrolysis of the putative intermediates were followed by TLC), yielded **13** as a single diastereomer of 88% ee in 72% yield.[63] Recrystallization afforded the chloro ketone of 95% ee in 66% yield. The configuration at C-4 of **13** was determined by NOE experiments. Chloro ketone **13** of 90% ee could also be obtained in a one-pot procedure in 78% yield by treatment of lithium enolate **11** with NCS at −105 °C in THF followed by a chromatographic separation of **13** and H-**10**.[64] During chromatography of **12** a partial epimerization at C-4 occurred, which was, however, of no consequence for the further steps. Reaction of chloro ketone **13** with *p*-toluenesulfonyl hydrazide[65a] gave the crystalline α-chloro tosylhydrazone **14**[65b] in 90% yield. Tosylhydrazone **14** has only a limited stability at room temperature but can be stored for a prolonged period of time at −30 °C without decomposition. A brief treatment of a suspension of **14** in ether with aqueous $NaHCO_3$ at room temperature led to a facile elimination of HCl and furnished the desired azoene Ts-**9** as a yellow solid in 90% yield. Azoene Ts-**9** is unstable at room temperature but can be stored at −70 °C for several weeks.

Enantioselective Synthesis of the Arylcopper Compound. Scheme 4 shows the sequence leading to the arylcopper compound Cu-**8d**. Reaction of *n*-pentylmagnesium bromide with aldehyde **15** afforded alcohol *rac*-**16** (90%),[66] which was oxidized with chromic acid in a mixture of water and ether[67] to

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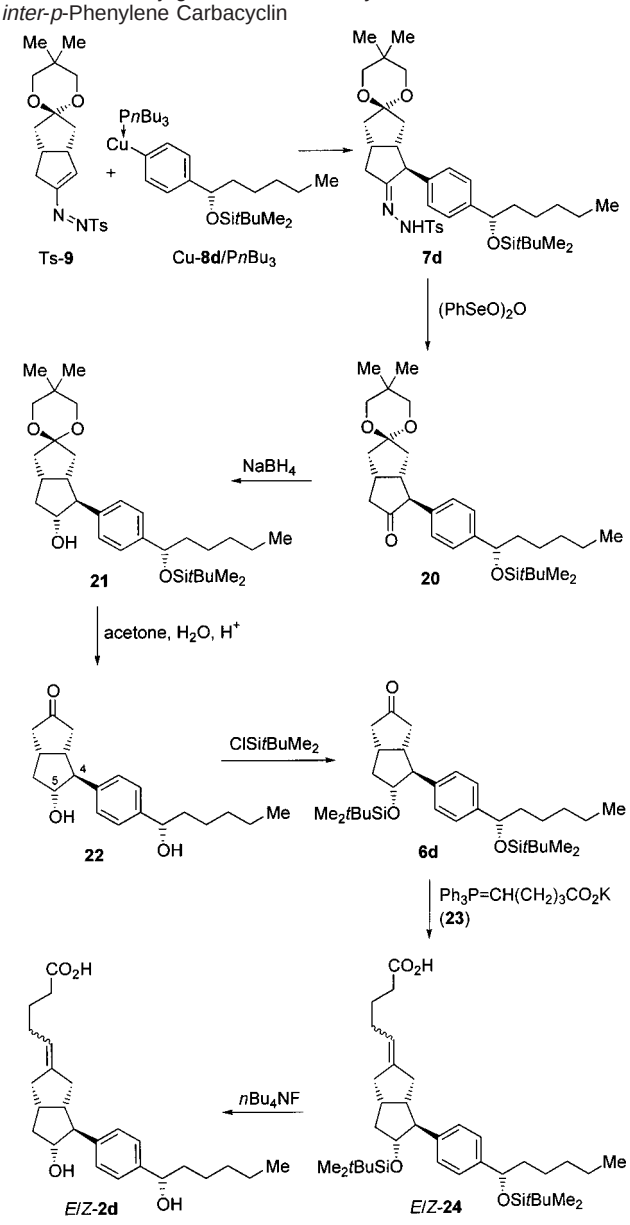
Scheme 5. Conjugate Addition and Synthesis of the *inter-p*-Phenylene Carbacyclin



ketone **17**[68] (90%). Enantioselective reduction of ketone **17** with (−)-diisopinocampheylchloroborane (**18**)[69] at −25 °C in THF by using a 10% excess of the reducing reagent afforded alcohol **16** of 98% ee, as determined by HPLC, in 85% yield. Since reduction of phenyl alkyl ketones with **18** uniformly affords the *S*-configured alcohols, we assign to **16** also the *S* configuration. Silyl protection of alcohol **16** with ClSi-*t*-$BuMe_2$ furnished silyl ether **19** (90%). Finally, lithiation of bromide **19** with 1 equiv of *t*-BuLi at −78 °C in ether and lithium−copper exchange through treatment of the corresponding aryllithium compound with 0.36 equiv of $[(nBu_3P)CuI]_4$[70] gave Cu-**8d**/P-*n*-Bu_3.

Conjugate Addition. As we had hoped, conjugate addition of the tributylphosphine complex of Cu-**8d** to azoene Ts-**9** proceeded readily with high diastereoselectivity (≥98%) by combining the two building blocks in a molar ratio of 1.1:1 (Scheme 5). Thus, treatment of azoene Ts-**9** with 1.1 equiv of Cu-**8d**/P*n*Bu_3 at −60 °C in ether/THF under homogeneous conditions furnished hydrazone **7d**[65b] in 80% yield after chromatographic purification. Selective unmasking of the carbonyl group at C-5 of **7d** was achieved by treatment of the hydrazone with benzeneseleninic anhydride[71] at room temperature, which afforded ketone **20**. Surprisingly, ketone **20** was unstable on silica gel. Thus, it was not purified but reduced directly with $NaBH_4$ at −40 °C in ethanol, which occurred with high diastereoselectivity (≥98%) and gave alcohol **21** in 59% yield based on hydrazone **7d**. The relative configurations of the stereogenic centers at C-4 and C-5 of **21** were determined by NOE experiments. This assignment was confirmed by an analysis of the ^1J couplings in the ^{1}H NMR spectrum of **21**.

For the attachment of the α-side chain acetal **21** was deprotected with *p*-TsOH in acetone and water, which gave under simultaneous deprotection of the hydroxy group the dihydroxy ketone **22**, admixed with 2,2-dimethylpropane-1,3-diol. Since the latter proved to be difficult to separate, diol **22** was silylated with ClSi-*t*-$BuMe_2$, which afforded bis(silyl) ether **6d** in 79% yield based on **20**. *E*-Selective Wittig olefination of ketone **6d** with 10 equiv of ylide **23**[72] at room temperature in glyme gave a mixture of the acids *E*-**24** and *Z*-**24** in a ratio of 72:28 in 72% yield. The *E*/*Z* ratio of **24** was determined by GC analysis of the corresponding methyl esters, which were obtained upon treatment of the acids with diazomethane. Finally, deprotection of the bissilyl ethers *E*/*Z*-**24** with NBu_4F afforded a mixture of the *inter*-phenylene carbacyclins *E*-**2d** and *Z*-**2d** in a ratio 72:28 in 85% yield. Since diastereomeric purity was not mandatory for the evaluation of the biological activity of *E*-**2d**, no attempts were made to separate the *E* and *Z* isomers or to synthesize *E*-**2d** stereoselectively. In vitro testing of *E*/*Z*-**2d** (72:28) as an inhibitor of ADP-induced human platelet aggregation revealed it to have an effect about 10 000-fold weaker than that of iloprost (**2b**) with an IC_{50} of > 10 μmol/L. A prostacyclin-like effect of *E*/*Z*-**2d** is thus questionable.

Conclusion

In conclusion, an enantioselective synthesis of 13,14-dinor-*inter-p*-phenylene carbacyclin by a new strategy based on the conjugate addition of an arylcopper compound to an azoene has been realized. The enantioselective synthesis of azoene Ts-**9** from ketone **4** and the conjugate addition of arylcopper compound Cu-**8d**/P-*n*-Bu_3 to the azoene are the cornerstones of this synthesis. Azoene Ts-**9** has the potential of serving as a building block for the synthesis of carbacyclin and isocarbacyclin derivatives, having ω-alkenyl side chains, since model studies revealed a facile conjugate addition of (1-alkenyl)copper compounds to the azoene.[73]

Experimental Section

General Comments and Materials. All reactions with organometallic reagents were carried out under argon in oven-dried glassware by using Schlenk and syringe techniques. Et_2O and THF were distilled from sodium−lead/benzophenone, CH_2Cl_2 and DMF were distilled from CaH_2, and EtOH was distilled from sodium. Bulk solvents for

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chromatography and extraction were distilled prior to use. Reagents and glyme were obtained from commercial sources and used without further purification unless otherwise stated. [(*n*-Bu_3P)CuI]$_4$ was prepared from CuI and *n*-Bu_3P according to the literature.[70] *n*-BuLi and *t*-BuLi were standardized by titration with diphenylacetic acid.[74] Analytical thin-layer chromatography (TLC) was performed on E. Merck precoated TLC plates (silica gel 60 F_{254}, layer thickness 0.2 mm). Gravitation column chromatography (denoted as chromatography) was performed with E. Merck silica gel 60 (0.063−0.200 mm). Melting points were determined with a Büchi 535 apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR 300, an Innova 400, or a Varian Unity 500 instrument. Chemical shifts are reported relative to TMS (δ 0.00 ppm) as internal standard with exception of those where [D_8]THF (δ 1.73 and 3.58 ppm for ^{1}H NMR; δ = 25.5 and 67.7 ppm for ^{13}C NMR) was used as the solvent. Splitting patterns in the ^{1}H NMR spectra are designated as s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; and m, multiplet. Peaks in the ^{13}C NMR spectra are denoted as "u" for carbons with zero or two attached protons or as "d" for carbons with one or three attached protons, as determined from the APT puls sequence. Solutions of (+)-Pr(tfc)$_3$ and Ag(fod) for the ^{1}H NMR shift experiments[75] were freshly prepared immediately before use. Low-resolution mass spectra were recorded on a Varian MAT 212 mass spectrometer, and high-resolution mass spectra on a Varian MAT 95 mass spectrometer. Optical rotations were measured with a Perkin-Elmer model 241 polarimeter at approximately 25 °C. Elemental analyses were performed by the Institut für Organische Chemie Microanalytical Laboratory.

(+)-(3′a*S*-*cis*)-Trimethyl[(3′,3′a,4′,6′a-tetrahydro-5,5-dimethylspiro-[1,3-dioxane-2,2′(1*H*)-pentalen]-5′-yl)oxy]silane (12). *N*-BuLi (90 mL of 1.55 M in hexanes, 140.95 mmol) was added dropwise at −78 °C to a suspension of (*R*,*R*)-bis(phenylethyl)amine hydrochloride (H-**10**·HCl)[76] (18.45 g, 70.47 mmol) in THF (300 mL). The mixture was then gradually warmed to room temperature, whereby a clear yellow solution of Li-**10**·LiCl was formed. Subsequently, the solution of Li-**10**·LiCl was cooled to −100 °C and a solution of ketone **4** (10.00 g, 44.58 mmol) in THF (120 mL) was added within 30 min. After the mixture was stirred at −100 °C for 40 min, $ClSiMe_3$ (9.70 g, 89.17 mmol) was added dropwise, and the mixture was stirred at this temperature for 30 min. The cooling bath was then removed, and saturated aqueous $NaHCO_3$ (6 mL) was added. Subsequently, the mixture was warmed to room temperature within 45 min and $MgSO_4$ was added. After the mixture was stirred for 30 min, it was filtered and the filtrate was concentrated in vacuo. The residue was diluted with pentanes (200 mL), whereby H-**10**·HCl precipitated, which was removed by filtration and treated further as described below. Then, the filtrate was concentrated in vacuo and the residue was purified by chromatography (hexanes/EtOAc, 9:1) (column: 5 cm i.d.,. 33 cm silica gel, which was preconditioned with hexanes/EtOAc, 9:1, flow rate 33 mL/min) to give the silyl enol ether **12** (10.40 g, 80%) as a colorless oil. The ee value of **12** was determined to be 90% by NMR shift studies using 100 mol % Ag(fod)/100 mol % (+)-Pr(tfc)$_3$ in $CDCl_3$ (^{1}H NMR, 300 MHz, δ 4.38 (4-H, *ent*-**12**), 4.44 (4-H, **12**)): R_f 0.66 (hexanes/EtOAc, 1:1); $[\alpha]_D$ +16.7 (*c* 1.00, acetone); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.20 (s, 9 H, $Si(CH_3)_3$), 0.95 (s, 3 H, $C(CH_3)_2$), 0.97 (s, 3 H, $C(CH_3)_2$), 1.52−1.60 (m, 2 H, 1-H, 3-H), 1.96−2.05 (m, 1 H, 6-H), 2.25−2.40 (m, 2 H, 3-H, 6-H), 2.50−2.68 (m, 2 H, 6-H, 6a-H), 3.05−3.12 (m, 1 H, 3a−H), 3.45 (s, 2 H, OCH_2), 3.48 (s, 2 H, OCH_2), 4.61 (m, 1 H, 4-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.00 (d), 22.57 (d), 30.13 (u), 35.57 (d), 39.95 (u), 40.18 (u), 41.22 (u), 43.22 (d), 71.47 (u), 72.80 (u), 107.27 (d), 108.91 (u), 152.76 (u); IR (neat) ν 2955 (vs), 2904 (s), 2852 (s), 1644 (s) cm^{-1}; MS (EI) *m*/*z* (relative intensity, %) 296 (M^+, 33), 224 (24), 209 (66), 206 (51), 181 (28), 168 (28), 167 (100), 154 (24), 128 (92), 75 (30), 74 (25), 73 (86), 69 (43). Anal. Calcd for $C_{16}H_{28}O_3Si$ (296.48): C, 64.82; H, 9.52. Found: C, 64.99; H, 9.53.

Recovery of (*R*,*R*)-Bis(phenylethyl)amine (H-10). The silica gel used in the purification of **12** was washed with THF (1000 mL). The washings were concentrated in vacuo, and the residue was combined with H-**10**·HCl obtained during isolation of **12**. The resulting mixture was suspended in 0.5 M aqueous HCl (200 mL), and the mixture was heated at reflux until a clear solution was obtained. Subsequently, the solution was cooled first to room temperature and then to 0 °C, whereby a white solid precipitated. Recrystallization of the solid from water gave H-**10**·HCl (12.95 g, 70%).

(−)-(3′a*S*,4′*R*,6′a*R*)-[4′-Chloro-1′,6′a,6′,3′a-tetrahydro-5,5-dimethylspiro[1, 3-dioxane-2,2′-(1′*H*)-pentalen]]-5′-one (13). A solution of *N*-chlorosuccinimide (4.64 g, 34.76 mmol) in CH_2Cl_2 (150 mL) was added at room temperature dropwise to a solution of the silyl enol ether **12** (9.80 g, 33.11 mmol) in CH_2Cl_2 (100 mL). After the mixture was stirred for 1 h at room temperature, it was concentrated in vacuo and the residue was diluted with pentanes (150 mL), whereby succinimide precipitated. The mixture was then filtered, the filtrate was concentrated at 25 °C in vacuo, and the residue was dissolved in THF (100 mL). The thus obtained solution was treated with water (5 mL) and three drops of acetic acid. After this mixture was stirred at room temperature for 2 h, it was concentrated in vacuo. The residue was extracted with hexanes (300 mL), and the combined organic phases were dried ($MgSO_4$). Then the organic phases were concentrated in vacuo to a volume of 80 mL and cooled first to −25 °C, whereby crystals were formed, and then to −78 °C for 24 h. Filtration and drying at room temperature in vacuo gave chloro ketone **13** (6.63 g, 66%) as white crystals. The ee value was determined to be 95% by GC on a permethyl β-cyclodextrin column (CP-Chirasil-Dex-CB, Chrompack) (**13**, 27.08 min; *ent*-**13**, 26.92 min): R_f 0.36 (hexanes/EtOAc, 1:1); mp 54 °C; $[\alpha]_D$ −27.6 (*c* 1.00, THF); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (s, 6 H, $C(CH_3)_2$), 1.92−1.97 (ddd, *J* = 13.7, *J* = 5.2, *J* = 1.3 Hz, 1 H, 1-H), 2.10−2.15 (ddd, *J* = 14.0, *J* = 4.4, *J* = 1.4 Hz, 1 H, 6-H), 2.20−2.28 (m, 3 H, 1-H, 3-H, 6-H), 2.70−2.77 (dd, *J* = 19.2, *J* = 10.2 Hz, 1 H, 3-H), 2.79−2.86 (m, 1 H, 3a−H), 2.91−2.99 (m, 1 H, 6a−H), 3.44 (s, 2 H, OCH_2) 3.47 (s, 2 H, OCH_2), 4.14 (d, *J* = 7.5 Hz, 1 H, 4-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.41 (d), 22.35 (d), 29.99 (u), 33.65 (d), 38.87 (u), 40.88 (u), 41.12 (u), 47.09 (d), 63.13 (d), 71.62 (u), 72.33 (u), 108.81 (u), 210.14 (u); IR (KBr) ν 3480 (m), 2957 (s), 2907 (s), 2869 (s), 1755 (vs), 1718 (m) cm^{-1}; MS (EI) *m*/*z* (relative intensity, %) 258 (M^+, 24), 224 (20), 223 (100), 181 (8), 155 (8), 69 (9), 56 (9). Anal. Calcd for $C_{13}H_{19}ClO_3$ (258.74) : C, 60.35; H, 7.40. Found: C, 59.98; H, 7.37.

(−)-*N*-{(3′a*S*,4′*R*,6′a*R*)-[4′-Chloro-1′,6′a,6′,3′a-tetrahydro-5,5-dimethylspiro[1,3-dioxane-2,2′-(1′*H*)-pentalen-5′-ylidene]]}-*N*′-(*p*-toluenesulfonyl)hydrazine (14). To a solution of chloro ketone **13** (2.50 g, 9.66 mmol) in Et_2O (80 mL) was added at 0 °C *p*-toluenesulfonyl hydrazide (1.90 g, 10.18 mmol). After the resulting white suspension was stirred at 0 °C for 48 h, it was concentrated in vacuo and the remaining white solid was washed with Et_2O (10 mL). Drying at room temperature in vacuo gave tosylhydrazone **14** (3.69 g, 90%) as a white solid: mp 72 °C (dec); $[\alpha]_D$ −42.1 (*c* 1.00, THF); ^{1}H NMR (500 MHz, CD_2Cl_2) δ 0.87 (s, 3 H, $C(CH_3)_2$), 0.90 (s, 3 H, $C(CH_3)_2$), 1.57 (dd, *J* = 11.0, *J* = 7.6 Hz, 1 H, 3-H), 1.82 (dd, *J* = 14.0, *J* = 3.0 Hz, 1 H, 1-H), 2.07−2.21 (m, 3 H, 1-H, 3-H, 6-H), 2.42 (s, 3 H, Tol), 2.59 (dd, *J* = 18.3, *J* = 10.5 Hz, 1 H, 6-H), 2.76−2.85 (m, 1 H, 3a-H), 2.92−3.02 (m, 1 H, 6a-H), 3.13−3.23 (m, 2 H, OCH_2), 3.73 (s, 2 H, OCH_2), 4.49 (s, 1 H, 4-H), 7.34 (m, 2 H, Tol), 7.48 (s, 1 H, N−H), 7.80 (m, 2 H, Tol); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 21.72 (d), 22.34 (d), 22.40 (d), 30.10 (u), 31.96 (u), 37.62 (d), 38.26 (u), 41.78 (u), 50.32 (d), 65.11 (d), 71.96, 72.37 (u), 109.19 (u), 128.19 (d), 129.98 (d), 135.71 (d), 144.83 (u), 163.06 (u); IR (KBr) ν 3224 (s), 2949 (s), 2869 (m), 1598 (m), 1419 (m), 1707 (s), 1348 (vs), 1164 (vs), 822 (s), 720 (s) cm^{-1}; MS (EI) *m*/*z* (relative intensity, %) 426 (M^+, 0.1), 208 (12), 207 (100), 128 (12), 121 (17), 93 (15), 91 (16), 79 (38). Anal. Calcd for

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$C_{20}H_{27}ClN_2O_4S$ (426.96): C, 56.26; H, 6.37; N, 6.56. Found: C, 55.92; H, 6.31; N, 6.39.

(−)-(3′a*S*-*cis*)-[3′,3′a,4′,6′a-Tetrahydro-5,5′-dimethylspiro[1,3-dioxane-2,2′(1′*H*)-pentalen-5′-yl]](*p*-toluenesulfonyl)diazene (Ts-9). Saturated aqueous $NaHCO_3$ (10 mL) was added at room temperature to a suspension of tosylhydrazone **14** (1.63 g, 3.82 mmol) in Et_2O (150 mL). After the mixture was shaken intensively for 3 min, the aqueous phase was separated and the yellow organic phase was washed twice with water, dried ($MgSO_4$), and concentrated at room temperature in vacuo. Drying of the residue at room temperature in vacuo gave azoene Ts-**9** (1.34 g, 90%) as a yellow solid containing 24 mg of Et_2O, which was stored at −70 °C: mp 70 °C (dec); $[\alpha]_D$ −11.1 (*c* 1.00, THF); ^{1}H NMR (400 MHz, C_6D_6) δ 0.66 (s, 3 H, $C(CH_3)_2$), 0.79 (s, 3 H, $C(CH_3)_2$), 1.26 (dd, J = 13.2, J = 6.9 Hz, 1 H, 3-H), 1.46 (dd, J = 13.7, J = 6.6 Hz, 1 H, 1-H), 1.84 (s, 3 H, Tol), 1.86−2.20 (m, 3 H, 1-H, 3-H, 6-H), 2.35−2.45 (m, 2 H, 6-H, 6a-H), 2.79−2.88 (m, 1 H, 3a-H), 3.07 (m, 2 H, OCH_2), 3.18 (s, 2 H, OCH_2), 6.53 (m, 1 H, 4-H), 6.76 (m, 2 H, Tol), 7.89 (m, 2 H, Tol); ^{13}C NMR (100 MHz, C_6D_6) δ 21.23 (d), 22.29 (d), 22.52 (d), 29.85 (u), 34.21 (u), 37.09 (d), 38.63 (u), 39.97 (u), 47.32 (d), 71.65 (u), 72.25 (u), 108.46 (u), 129.84 (d), 130.66 (d), 131.82 (u), 145.19 (u), 156.41 (d), 156.66 (u); IR (KBr) ν 3431 (m), 2953 (s), 2866 (m), 2188 (w), 1598 (w, br) cm^{-1}; MS (CI) *m*/*z* (relative intensity, %) 365 (8), 364 (21), 363 (100), 207 (32); HRMS calcd for $C_{13}H_{19}O_2$ ($M^+ - C_7H_7N_2O_2S$) 207.138 505, found 207.138 640.

(−)-*N*-{(3′a*S*,4′*S*,6′a*R*)-4′-[4-((*S*)-1″-(*tert*-Butyldimethylsilanyloxy)hexyl) phenyl]-1′,6′a,6′,3′a-tetrahydro-5,5-dimethylspiro[1,3-dioxane-2,2′(1′*H*)-penta len-5′-ylidene]}-*N*′-(*p*-toluenesulfonyl)hydrazine (7d). *t*-BuLi (2.13 mmol, 1.44 mL of 1.48 M in pentanes) was added at −78 °C to a solution of bromide **19** (793 mg, 2.17 mmol) in Et_2O (6 mL). After the mixture was stirred for 30 min at −78 °C, the cold solution was added at −10 °C by means of a double-tipped ended needle to a solution of $[(n\text{-}Bu_3P)CuI]_4$ (923 mg, 0.59 mmol) in Et_2O (6 mL). The resulting yellow solution of Cu-**8d**/P-*n*-Bu_3 was stirred at −10 °C for 40 min, and then THF (12 mL) was added and the solution was cooled to −60 °C. Subsequently, a solution of azoene Ts-**7** (758 mg, 1.94 mmol) in THF (12 mL), which had been precooled to −60 °C, was added at −60 °C under stirring to the solution of Cu-**9d**/P-*n*-Bu_3 by means of a double-tipped ended needle. After the resulting mixture was stirred for 30 min at −60 °C, water (3 mL) was added and the mixture was warmed to room temperature. Subsequently, a mixture of saturated aqueous NH_4Cl and concentrated aqueous NH_3 (40 mL, 10:1) was added and the solution was stirred for 1 h. The organic phase was then separated, and the aqueous phase was successively extracted with THF (50 mL) and Et_2O (50 mL). The combined organic phases were concentrated in vacuo, and the residue was dissolved in Et_2O (80 mL). Then, the resulting solution was treated with a mixture of saturated aqueous NH_4Cl and concentrated aqueous NH_3 (10 mL, 10:1) and the mixture was stirred for 1 h. Subsequently, the organic phase was separated, dried ($MgSO_4$), and concentrated in vacuo. Purification of the residue by chromatography (hexanes/EtOAc, first 10:1 and then 1:1) gave hydrazone **7d** (1.06 g, 80%) as a light-yellow flaky solid: mp 57 °C (dec); R_f 0.42 (hexanes/EtOAc, 1:1): $[\alpha]_D$ −75.0 (*c* 1.00, THF); ^{1}H NMR (400 MHz, [D_8]THF) δ −0.14 (s, 3 H, $Si(CH_3)_2$), 0.06 (s, 3 H, $Si(CH_3)_2$), 0.86−0.92 (m, 18 H, $SiC(CH_3)_3$, $C(CH_3)_2$, CH_3), 1.26−1.33 (m, 6 H, 3′-H, 4′-H, 5′-H), 1.41 (m, 1 H, 2'-H), 1.59 (m, 1 H, 2′-H), 1.67−1.71 (m, 1 H, 6-H), 1.84 (dd, J = 13.7, J = 4.9 Hz, 1 H, 3-H), 2.15 (dd, J = 13.7, J = 7.5 Hz, 1 H, 3-H), 2.25−2.30 (m, 2 H, 1-H, 6-H), 2.37 (s, 3 H, Tol), 2.52−2.61 (m, 2 H, 1-H, 3a-H), 2.65−2.72 (m, 1 H, 6a-H), 3.36−3.43 (m, 4 H, OCH_2), 3.59 (d, J = 8.5 Hz, 1 H, 4-H), 4.66−4.69 (m, 1 H, 1′-H), 6.98 (d, J = 8.2 Hz, 2 H, *o*′-Ph), 7.14−7.19 (m, 4 H, *m*-, *m*′-Ar), 7.59−7.62 (m, 2 H, *o*-Ar), 8.78 (s, 1 H, NH); ^{13}C NMR (100 MHz, [D_8]THF) δ −5.24 (d), −4.77 (d), 13.91 (d), 18.37 (u), 21.02 (d), 22.12 (d), 22.22 (d), 22.99 (u), 25.74 (u), 25.85 (d), 30.05 (u), 32.27 (u), 33.94 (u), 38.36 (d), 39.71 (u), 41.46 (u), 42.08 (u), 49.04 (d), 55.91 (d), 71.79, 72.32 (u), 75.32 (d), 110.14 (u), 125.86 (d), 128.11 (d), 128.36 (d), 129.11 (d), 137.91 (d), 140.76 (u), 142.82 (u), 144.02 (u), 167.29 (u); IR (KBr) ν 3448 (m, br), 3218 (m), 2955 (vs), 2931 (vs), 2858 (vs), 1741 (m) cm^{-1}; MS (EI) *m*/*z* (relative intensity, %) 683 (M^+, 3), 627 (15), 626 (35), 625 (78), 528 (20), 527 (49), 395 (24), 309 (42), 297 (40), 281 (45), 239 (32), 223 (16), 215 (25), 213 (33), 212 (22), 211 (100), 169 (25), 168 (11), 167 (16), 155 (14), 149 (39); HRMS calcd for $C_{34}H_{49}N_2O_5SSi$ ($M^+ - C_4H_9$) 625.313 149, found 625.313 324.

(3′a*S*,4′*S*,6′a*R*)-[4′-[4-((*S*)-1″-(*tert*-Butyldimethylsilanyloxy)hexyl)-phenyl]-1′,6′a,6′,3′a-tetrahydro-5,5-dimethylspiro[1,3-dioxane-2,2′]]-pentalen-5′-one (20) and (+)−(3′a*S*,4′*S*,5′*R*,6′a*R*)-[4′-[4-((*S*)-1″-(*tert*-butyldimethylsilanyloxy)hexyl)phenyl]-1′,6′a,6′,3′a-tetrahydro-5,5-dimethylspiro[1,3-dioxane-2,2′]]pentalen-5′-ol (21). Benzeneseleninic anhydride (0.55 g, 1.54 mmol) was added at room temperature portionwise to a solution of tosylhydrazone **7d** (1.00 g, 1.47 mmol) in THF (50 mL), whereby gas evolution occurred. After the yellow solution was stirred at room temperature for 1 h, saturated aqueous $NaHCO_3$ (2 mL) was added and the mixture was extracted with hexanes (100 mL). Drying of the combined organic phases ($MgSO_4$) and evaporation of the solvent in vacuo gave crude ketone **20** as a brown oil. This material was dissolved in ethanol (100 mL) and the solution treated at −40 °C portionwise with $NaBH_4$ (168 mg, 4.41 mmol). After the mixture was stirred at −40 °C for 7 h, saturated aqueous NH_4Cl (5 mL) was added and the solution was extracted with Et_2O (200 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by chromatography (hexanes/EtOAc, 3:1) gave alcohol **21** (515 mg, 59% based on **7d**) as a colorless oil: R_f 0.27 (hexanes/EtOAc, 3:1); $[\alpha]_D$ +46.4 (*c* 1.20, THF); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.14 (s, 3 H, $Si(CH_3)_2$), 0.16 (s, 3 H, $Si(CH_3)_2$), 1.02 (m, 12 H, $SiC(CH_3)_3$, CH_3), 1.07 (s, 3 H, $C(CH_3)_2$), 1.14 (s, 3 H, $C(CH_3)_2$), 1.36−1.50 (m, 6 H, 3′-H, 4′-H, 5′-H), 1.68−1.76 (m, 2 H, 6-Hβ, 2′-H), 1.76−1.84 (m, 1 H, 2′-H), 1.85 (s, 1 H, OH), 2.02 (m, 2 H, 1-H, 3-H), 2.24 (m, 1 H, 3-H), 2.37 (dd, J = 13.3, J = 8.7 Hz, 1 H, 1-H), 2.50 (m, 1 H, 6-H), 2.64−2.78 (m, 2 H, 3a-H, 6a-H), 2.86 (t, J = 9.4 Hz, 1 H, 4-H), 3.60 (s, 2 H, OCH_2), 3.66 (s, 2 H, OCH_2), 4.26 (td, J = 9.9, J = 6.3 Hz, 1 H, 5-H), 4.75 (dd, J = 7.5, J = 5.0 Hz, 1 H, 1′-H), 7.31 (d, J = 8.2 Hz, 2 H, *o*′-Ar), 7.38 (d, J = 8.2 Hz, 2 H, *m*′-Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.90 (d), −4.54 (d), 14.04 (d), 18.21 (u), 22.46 (d), 22.58 (d), 25.24 (u), 25.84 (d), 30.06 (u), 31.73 (u), 35.44 (d), 38.25 (u), 40.85 (u), 41.15 (u), 40.92 (u), 46.00 (d), 60.28 (d), 71.92 (u), 71.99 (u), 74.66 (d), 79.68 (d), 110.05 (u), 125.92 (d), 126.98 (d), 140.02 (u), 144.20 (u); IR (KBr, $CHCl_3$) ν 3420 (m), 2955 (vs), 2931 (vs), 2857 (vs), 1738 (m) cm^{-1}; MS (EI) *m*/*z* (relative intensity, %) 516 (M^+, 1), 498 (12), 459 (26), 445 (43), 441 (11), 427 (29), 373 (26), 367 (18), 359 (13), 355 (21), 281 (100), 273 (14), 223 (13), 211 (17); HRMS calcd for $C_{31}H_{50}O_3Si$ ($M^+ - H_2O$) 498.352 924, found 498.352 833.

(3a*S*,4*S*,5*R*,6a*R*)-5-Hydroxy-4-[4-((S)-1′-hydroxyhexyl)phenyl]-hexahydropentalen-2-one (22). *p*-Toluenesulfonic acid (80 mg) was added at room temperature to a solution of acetal **21** (500 mg, 0.97 mmol) in acetone (40 mL) and water (4 mL). After the mixture was stirred at room temperature for 12 h, saturated aqueous $NaHCO_3$ was added and the mixture was extracted with Et_2O (150 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by chromatography (Et_2O) gave a mixture (335 mg) of diol **22** and 2,2-dimethylpropane-1,3-diol in a molar ratio of 61:39 as a white solid: R_f 0.21 (Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (s, 2,2-dimethypropane-1,3-diol), 0.87 (t, J = 6.9 Hz, 3 H, CH_3), 1.25−1.31 (m, 6 H, 5′-H, 4′-H, 3′-H), 1.51−1.58 (m, 1 H, 6-H), 1.60−1.80 (m, 2 H, 2′-H), 2.12−2.22 (m, 2 H, 3-H, 1-H), 2.34−2.41 (m, 1 H, 3-H), 2.52−2.60 (m, 3 H, 1-H, 6-H, 4-H), 2.75−2.87 (m, 2 H, 3a−H, 6a−H), 3.38 (s, 2,2-dimethylpropane-1,3-diol), 4.23 (td, J = 8.9, J = 7.2 Hz, 5-H), 4.58 (dd, J = 7.7, J = 5.8 Hz, 1 H, 1-H), 7.18 (d, J = 8.2 Hz, 2 H, *o*′-Ar, 7.27 (d, J = 8.2 Hz, 2 H, *m*′-Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.04 (d), 21.72 (2,2-dimethylpropane-1,3-diol, d), 22.55 (u), 25.52 (u), 31.67 (u), 35.02 (d), 36.28 (2,2-dimethyl-propane-

1,3-diol, u), 38.94 (u), 41.21 (u), 42.90 (u), 45.65 (u), 44.83 (d), 60.06 (d), 71.17 (2,2-dimethyl-propane-1,3-diol, u), 74.16 (d), 79.50 (d), 126.23 (d), 127.52 (d), 139.79 (u), 143.61 (u), 219.79 (u); IR (KBr) ν 3338 (s, br), 2956 (s), 2930 (vs), 2862 (s), 1737 (vs) cm^{-1}; MS (EI) *m*/*z* (relative intensity, %) 316 (M^+, 3), 246 (16), 245 (100).

(−)-(3a*S*,4*S*,5*R*,6a*R*)-4-{4-[(*S*)-1′-(tert-Butyldimethylsilanyloxy)-hexyl]phenyl}-5-[*tert*-butyldimethylsilanyloxy]hexahydropentalen-2-one (6d). *tert*-Butyldimethylsilyl chloride (472 mg, 3.13 mmol) and imidazole (427 mg, 6.26 mmol) were added at room temperature to a solution of a mixture of diol **22** and 2,2-dimethylpropane-1,3-diol (335 mg) in a molar ratio of 61:39 in DMF (30 mL). After the mixture was stirred at 50 °C for 2 h, it was cooled to room temperature and water (5 mL) was added. The mixture was then extracted with Et_2O, and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by chromatography (hexanes/EtOAc, 2:1) gave the silyl ether **6d** (423 mg, 88%) as a white solid: mp 85 °C; R_f 0.55 (hexanes/EtOAc, 4:1); $[\alpha]_D$ −39.8 (*c* 1.00, THF); ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.34, −0.24, −0.17, −0.03 (4 s, 12 H, $SiMe_2$), 0.72 (s, 9 H, $SiC(CH_3)_3$, 0.86 (s, 9 H, $SiC(CH_3)_3$), 0.83 (m, 3 H, 6′-H), 1.16−1.36 (m, 6 H, 3′-H, 4′-H, 5′-H), 1.50−1.58 (m, 2 H, 6-H, 2′-H), 1.60−1.68 (m, 1 H, 2′-H), 2.16−2.27 (m, 2 H, 1-H, 3-H), 2.36−2.48 (m, 2 H, 1-H, 6-H), 2.56−2.67 (m, 2 H, 3-H, 4-H), 2.76−2.84 (m, 2 H, 3a−H, 6a−H), 4.09 (dt, J = 7.0, J = 8.2 Hz, 1 H, 5-H), 4.58 (dd, J = 7.0, J = 5.3 Hz, 1 H, 1′-H), 7.09 (d, J = 8.2 Hz, 2 H, *o*′-Ar), 7.19 (d, J = 8.2 Hz, 2 H, *m*′-Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.14 (d), −5.10 (d), −4.93, −4.57 (d), 14.03 (d), 17.92 (u), 18.22 (u), 22.59 (u), 25.19 (u), 25.66 (d), 25.83 (d), 31.73 (u), 35.38 (d), 40.99 (u), 42.39 (u), 43.40 (u), 43.73 (d), 45.72 (u), 60.50 (d), 74.75 (d), 81.11 (d), 125.70 (d), 127.33 (d), 139.60 (u), 144.24 (u), 219.77 (u); IR (KBr) ν 2955 (vs), 2930 (vs), 2857 (s), 1726 (vs) cm^{-1}; MS (EI) *m*/*z* (relative intensity, %) 530 (1), 489 (13), 488 (34), 487 (100), 473 (20), 355 (13). Anal. Calcd for $C_{32}H_{56}O_3Si_2$ (544.96): C, 70.53; H, 10.36. Found: C, 70.25; H, 10.11.

(*E*)- and (*Z*)-5-{(3′a*S*,4′*S*,5′*R*,6′a*S*)-4′-{4-[(*S*)-1″-(*tert*-Butyldimethylsilanyloxy)hexyl]phenyl}-5′-[*tert*-butyldimethylsilanyloxy]hexahydro-pentalen-2′-ylidene}pentanoic Acid (*E*-24 and *Z*-24). To a suspension of (4-carboxybutyl)triphenylphosphonium bromide (1.627 g, 3.67 mmol) in glyme (20 mL) was added at room temperature KO-*t*-Bu (823 mg, 7.34 mmol). After the deep orange suspension of **23** was stirred at room temperature for 30 min, a solution of ketone **6d** (200 mg, 0.37 mmol) in Et_2O (4 mL) was added and the mixture was stirred for 12 h at room temperature. Then, saturated aqueous NH_4Cl (2 mL) was added and the mixture was extracted with Et_2O (4 × 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by chromatography (hexanes/EtOAc, 4:1) gave a mixture of acids *E*-**24** and *Z*-**24** (167 mg, 72%) in a ratio of 72:28 as a colorless oil: R_f 0.38 (hexanes/EtOAc, 4:1); $[\alpha]_D$ +70.0 (*c* 1.50, THF); ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.22 (s, 3 H, $Si(CH_3)_2$), −0.14 (s, 3 H, $Si(CH_3)_2$), 0.14 (s, 3 H, $Si(CH_3)_2$), 0.15 (s, 3 H, $Si(CH_3)$), 0.85 (s, 9 H, $SiC(CH_3)_3$), 1.02 (s, 9 H, $SiC(CH_3)_3$), 0.99 (m, 3 H, 6′-H), 1.32−1.54 (m, 7 H, 3′-H, 4′-H, 5′-H, 6-H), 1.64−1.91 (m, 4 H, 2′-H, C*H*$_2$CH$_2$COOH), 2.14−2.32 (m, 4 H, 1-H, C*H*$_2$CH$_2$-CH$_2$COOH), 2.36−2.74 (m, 8 H, 3-H, 4-H, 6-H, 3a-H, 6a-H, C*H*$_2$-COOH), 4.05 (ddd, J = 9.6, J = 9.1, J = 6.9 Hz, 1 H, 5-H), 4.73 (dd, J = 7.0, J = 5.4 Hz, 1 H, 1′-H), 5.36 (m, 1 H, =CH), 7.26 (d, J = 8.2 Hz, 2 H, *o*′-Ar), 7.32 (d, J = 8.0 Hz, 2 H, *m*′-Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.15 (d), −5.07 (d), −4.94 (d), −4.53 (d), 14.05 (d), 17.99 (u), 18.24 (u), 22.61 (u), 24.79 (u), 25.24 (u), 25.71 (u), 25.85 (d), 28.69 (u), 31.76 (u), 33.39 (u), 35.85 (u), 37.73 (d), 38.90 (u), 41.06 (u), 42.65 (u), 45.89 (d), 59.36 (d), 74.88 (d), 80.55 (d), 120.29 (d), 125.42 (d), 127.62 (d), 140.83 (u), 143.02 (u), 143.68 (u), 179.20 (u); IR ($CHCl_3$) ν 2954 (vs), 2930 (vs), 2857 (s), 1710 (s) cm^{-1}; MS (CI) *m*/*z* (relative intensity, %) 629 (M^+, 31), 553 (22), 498 (41), 497 (100), 481 (11), 440 (14), 439 (44), 421 (10), 407 (12), 366 (18), 365 (65), 285 (34), 283 (44), 257 (12), 248 (54), 133 (41). Anal. Calcd for $C_{37}H_{64}O_4Si_2$ (629.08): C, 70.64; H, 10.25. Found: C, 70.30; H, 10.54.

(*E*)- and (*Z*)-5-{(3′a*S*,4′*S*,5′*R*,6′a*S*)-5′-Hydroxy-4′-[4-((S)-1″-hydroxyhexyl)phenyl]hexahydropentalen-2′-ylidene}pentanoic Acid (*E*-2d and *Z*-2d). *n*-$Bu_4NF{\cdot}H_2O$ (1.50 mmol, 1.50 mL of 1.0 M in THF) was added at room temperature to a solution of a mixture of acids *E*-**24** and *Z*-**24** (155 mg, 0.25 mmol) in a ratio of 72:28 in THF (20 mL). After the mixture was stirred at 35 °C for 24 h, water (5 mL) was added and the mixture was extracted with EtOAc (5 × 20 mL). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by chromatography (hexanes/EtOAc/HOAc, 20:20:1) gave a mixture of acids *E*-**2d** and *Z*-**2d** (84 mg, 85%) in a ratio of 72:28 as a colorless oil: R_f 0.50 (hexanes/EtOAc/AcOH, 20:20:1); $[\alpha]_D$ +67.2 (*c* 1.25, THF); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80 (m, 3 H, 6′-H), 1.18−1.44 (m, 7 H, 5′-H, 4′-H, 3′-H, 6-H), 1.62−1.82 (m, 4 H, 2′-H, C*H*$_2$CH$_2$COOH), 2.01−2.19 (m, 5 H, 3-H, 1-H, C*H*$_2$-CH$_2$CH$_2$COOH), 2.25−2.60 (m, 7 H, 3-H, 4-H, 6-H, 3a-H, 6a-H, C*H*$_2$-COOH), 4.07 (ddd, J = 9.6, J = 9.3, J = 6.9 Hz, 1 H, 5-H), 4.61 (m, 1 H, 1′-H), 5.26 (m, 1 H, =CH), 7.20 (d, J = 8.2 Hz, 2 H, *o*′-Ar), 7.27 (d, J = 7.7 Hz, 2 H, *m*′-Ar); ^{13}C NMR (100 MHz, $CDCl_3$) for *E*-**2d** δ 14.04 (d), 22.55 (u), 24.78 (u), 25.54 (u), 28.63 (u), 31.70 (u), 33.39 (u), 35.80 (u), 37.58 (d), 38.61 (u), 38.83 (u), 41.45 (u), 47.32 (d), 59.24 (d), 74.40 (d), 78.93 (d), 120.86 (d), 126.06 (d), 127.77 (d), 141.09 (u), 142.39 (u), 143.02 (u), 178.55 (u); ^{13}C NMR (100 MHz, $CDCl_3$) for *Z*-**2d** δ 24.78 (u), 28.64 (u), 33.09 (u), 36.72 (d), 41.20 (u), 48.17 (d), 60.08 (d), 120.76 (d), 126.13 (d), 142.47 (u), 178.60 (u); IR ($CHCl_3$) ν 3382 (m, br), 3016 (m), 2954 (s), 2932 (s), 2860 (s), 1709 (s) cm^{-1}; MS (CI) *m*/*z* (relative intensity, %) 401 (M^+, 24), 384 (23), 383 (100), 366 (14), 365 (59), 163 (15), 161 (20), 148 (42), 119 (42); HRMS calcd for $C_{25}H_{32}O_2$ (M^+ − 2 H_2O) 364.240 230, found 364.240 367.

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Supporting Information Available: Experimental procedures for *rac*-**16**, **16**, **17**, and **19** and copies of ^{1}H NMR spectra of *E*/*Z*-**2d**, Ts-**9**, **7d**, **21**, and **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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