Total Synthesis of Colombiasin A and Determination of Its Absolute Configuration

K. C. Nicolaou,* Georgios Vassilikogiannakis, Wolfgang Mägerlein, and Remo Kranich[a]

Abstract: The total synthesis of the recently reported marine natural product colombiasin A (**1**) and determination of its absolute configuration are reported. Two Diels–Alder cycloadditions and a palladium-catalyzed rearrangement are employed as key reactions to construct the tetracyclic framework of the target molecule. The enantioselective synthesis of colombiasin A utilizes Mikami's [(*S*)-BINOL-$TiCl_2$] catalyst to asymmetrically introduce the first chiral center during the initial Diels–Alder reaction and, in conjunction with X-ray crystallographic analysis of a bromine containing derivative, led to the assignment of the absolute configuration of the natural product.

Keywords: absolute configuration · cycloaddition · natural products · polycycles · total synthesis

Introduction

Among the many recently discovered natural products, colombiasin A (**1**, Figure 1) stands out for its aesthetically pleasing and synthetically challenging molecular architecture. Isolated by Rodríguez and Ramírez and reported in 2000,[1] this novel diterpene was found in biologically active extracts (against *Mycobacterium tuberculosis* H37Rv) obtained from the gorgonian octacoral *Pseudopterogorgia elisabethae*, collected off San Andres Island, Colombia. Based on spectroscopic means, its structural elucidation revealed a tetracyclic skeleton possessing unusual connectivities, and carrying two conjugated carbonyl groups, two double bonds, one hydroxy group and four methyl residues. Its six stereogenic centers include two adjacent quaternary carbons, whose construction may require special attention. An intriguing proposal[1] relating to the possible biosynthesis of colombiasin A (**1**) connected its structure with that of elisabethin A, another diterpene isolated from *Pseudopterogorgia elisabethae*.[2]

Despite the elegant structural studies by the isolation team, however, the absolute stereochemistry of colombiasin A remained unknown. A recently published preliminary communication[3] from these laboratories reported the first total synthesis of (±)-colombiasin A. In this article, we describe the

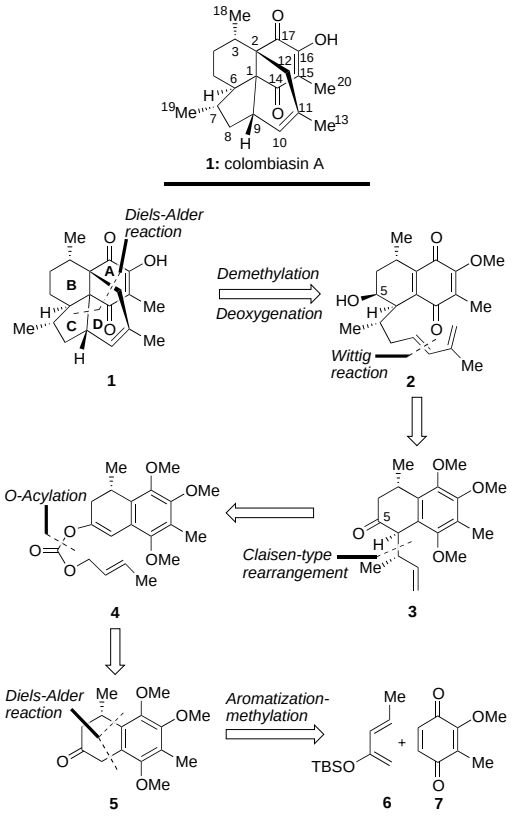

Figure 1. Retrosynthetic analysis of colombiasin A (**1**).

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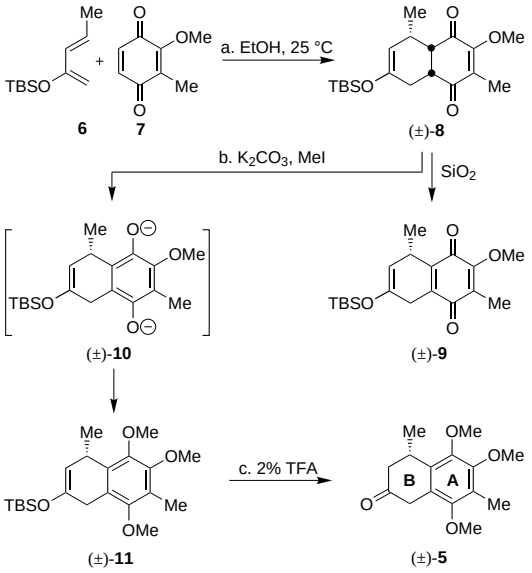
full details of our investigations that led to the total synthesis of both racemic and enantiomerically pure colombiasin A and the determination of its absolute configuration.

Results and Discussion

Retrosynthetic analysis and strategy: Despite its mystique, the structure of colombiasin A (**1**) reveals an intriguing clue as to a possible retrosynthetic disconnection: The cyclohexene ring fused onto a "semiquinone" leaves little doubt as to the viability of the intramolecular Diels–Alder reaction as a means to be used towards its construction. Thus, disconnection of the carbon–carbon bonds indicated in structure **1** (C_2–C_{12} and C_1–C_9, Figure 1) leads to diene-quinone **2** as a possible precursor for **1**. The presence of the superfluous hydroxyl group in **2** was meant to be only temporary and its introduction was for the purpose of facilitating this intermediate's construction. This handle, however, also offers an opportunity for analogue generation. In addition to providing a direct access to the entire skeletal framework of colombiasin A (**1**), this fruitful disassembly (**1** ⇨ **2**) also accommodates the construction of both quaternary carbons of the targeted molecule. Continuing with the retrosynthesis, precursor **2** is simplified by a retro-Wittig olefination reaction which, upon further manipulation at C_5, leads to potential intermediate **3**. This simplification ensures possible pathways to reach advanced intermediate **2** from rather simple starting materials and in relatively short order. Thus, the origins of **3** can be traced back, by a Claisen-type rearrangement, to enol-carbonate **4**. The latter intermediate (**4**) is envisioned to arise from ketone **5** by O-acylation. And finally, **5** can be connected from diene **6** and quinone **7** through an intermolecular Diels–Alder reaction, followed by an aromatization–methylation sequence.

Following this retrosynthetic analysis, a strategy emerged having a quinone moiety as the central cornerstone and the Diels–Alder reaction as the main vehicle for constructing the skeleton of colombiasin A. Thus, upon the initial, intermolecular Diels–Alder reaction, the quinone moiety is masked as an aromatic system until it is needed again at a later stage for the second, this time intramolecular Diels–Alder reaction, at which time it is regenerated to perform its function. An advantage of this strategy was the opportunity it offered for an enantioselective total synthesis, for it was considered possible to induce significant asymmetric induction by calling upon an enantiomerically pure Lewis acid to serve as a catalyst for the first Diels–Alder reaction. The execution of this plan proceeded with its share of intrigue as will be described below.

First-generation approach towards colombiasin A—Arrival at 7-*epi*-colombiasin A: The first-generation strategy towards colombiasin A involved racemic materials. Our journey to racemic colombiasin A [(±)-**1**] had as its first destination the AB system (±)-**5** (Scheme 1). The aromatic ring of (±)-**5** provides a masked form of a quinone moiety. The Diels–Alder cycloaddition of diene **6** to quinone **7**[4] proceeded



Scheme 1. Construction of AB ring system (±)-**5**. a) EtOH, 25 °C, 2 h; b) K_2CO_3 (5.0 equiv), MeI (20 equiv), acetone, reflux, 48 h; c) 2% TFA in CH_2Cl_2, 25 °C, 2 h, 70% over three steps. TFA = trifluoroacetic acid; TBS = *tert*-butyldimethylsilyl.

smoothly in EtOH at 25 °C to afford exclusively the rather labile *endo*-adduct (±)-**8**, which had the expected regiochemistry, based on the fact that one of the two carbonyl groups of quinone **7** is part of a vinylogous ester. Quinone **7** was obtained by *ortho*-methylation of 1,2,4-trimethoxybenzene,[5] followed by oxidative demethylation using AgO/HNO_3.[6] Since (±)-**8** was easily oxidized to the bicyclic quinone (±)-**9** during silica gel chromatographic purification, we decided to proceed to the next stage of the synthesis without purification. Thus, (±)-**8** was isomerized to the corresponding quinol derivative (±)-**10** (K_2CO_3), which was methylated in situ (MeI) to afford the corresponding dimethyl ether (±)-**11**. Acidic hydrolysis (TFA) of the resulting TBS-enol ether (±)-

Abstract in Greek:

Στην συγκεκριμένη εργασία περιγράφεται η ολική σύνθεση του πρόσφατα απομονωμένου θαλάσσιου φυσικού προϊόντος (-)-κολομβιασίνης Α και ο προσδιορισμός της έως σήμερα άγνωστης απόλυτης στερεοδομής του. Μία διαμορική Diels-Alder κυκλοπροσθήκη, μια καταλυτική (Pd^0) σιγματροπική μετάθεση, και μια ενδομοριακή Diels-Alder κυκλοπροσθήκη είναι τα στάδια κλειδιά για την οικοδόμηση του αρχιτεκτονικά πολύπλοκου τετρακυκλικού σκελετού του μορίου στόχου. Για τον εναντιοεκλεκτικό σχηματισμό του πρώτου από τα έξι χειρόμορφα κέντρα της κολομβιασίνης Α και κατ' επέκταση τη σύνθεση του φυσικού εναντιομερούς της, το σύμπλοκο [(*S*)-BINOL-$TiCl_2$] χρησιμοποιήθηκε ως καταλύτης της πρώτης (διαμοριακής) Diels-Alder αντίδρασης. Η απόλυτη στερεοδομή του φυσικού προϊόντος προσδιορίστηκε αναμφίβολα, μέσω της κρυσταλλογραφικής ανάλυσης ενός ενδιαμέσου, κρυσταλλικού βρώμο-παραγώγου.

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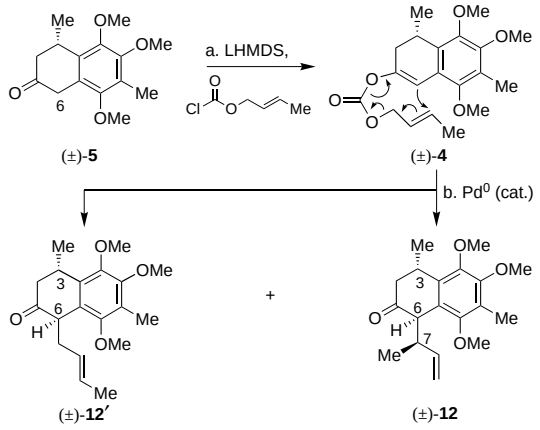
11 gave rise to aromatic ketone (±)-**5** in 70% overall yield for the three steps (for abbreviations of reagents and protecting groups see legends in schemes).

Having established the foundation of the AB ring system of colombiasin A, the next objective was the stereoselective introduction of the requisite side chain at C_6 of ketone (±)-**5**, for the next planned intramolecular Diels–Alder reaction. Not surprisingly, several attempts for direct alkylation of ketone (±)-**5** utilizing secondary halides (e.g. 3-bromo-1-butene and 2-methyl-6-iodo-1,3-heptadiene) as alkylating agents failed. We, therefore, set out to establish the requisite C_6–C_7 bond by intramolecular Pd-catalyzed allylic alkylation.[7] This reaction is formally considered as a sigmatropic rearrangement equivalent (Claisen rearrangement) based on the nature of both the starting material and the final product (Scheme 2). A major issue shadowing this proposition, however, was the relative configuration of the two newly formed stereogenic centers in the anticipated product. The precursor of this Pd-catalyzed alkylation was prepared in 94% yield by O-acylation of the enolate derived, regiospecifically, from ketone (±)-**5** (LHMDS) with crotyl chloroformate.[8] Upon exposure of the resulting enol carbonate (±)-**4** to catalytic amounts of different palladium complexes and phosphorus ligands (see Scheme 2 and Table 1), both α-allylated ketones



Scheme 2. Introduction of the side chain at C_6 by Pd-mediated allylic alkylation. a) LHMDS (1.2 equiv), THF, −78 °C, 1 h; then crotyl chloroformate (1.4 equiv), −78 → 25 °C, 30 min, 94%; b) see Table 1; LHMDS = lithium bis(trimethylsilyl)amide.

(±)-**12** and (±)-**12′** were obtained. These compounds could not be separated chromatographically and their ratio was determined by ^{1}H NMR spectroscopy. Fine tuning of the reaction led from an undesirable ratio of (±)-**12**:(±)-**12′** = 1:4 {[$Pd(OAc)_2$], $P(OiPr)_3$} to the satisfactory ratio of 2.4:1 [$Pd(PPh_3)_4$] (see Scheme 2 and Table 1). These observations can be mechanistically rationalized by assuming an oxidative addition of a PdL_n^0 species (L = ligand) to the crotyl moiety of enol carbonate (±)-**4**, leading to a cationic *syn*-[Pd(η^3-crotyl)L_2] complex (see below, intermediate **B**, Scheme 5) and an enolate anion after extrusion of CO_2.[9] The regioselectivity of the attack of this enolate (nucleophile) on the cationic crotyl Pd complex (substituted versus unsubstituted terminus) determines the (±)-**12**:(±)-**12′** ratio. In general, the nucleophilic attack takes place predominantly at the less sterically hindered, unsubstituted allyl terminus (especially in the case of Pd complexes) with the linear olefin being formed preferentially,[10] as observed in the presence of the phosphite ligand $P(OiPr)_3$ (entry 1, Table 1). However, in the case of the less basic (i.e., weaker σ-electron donating)[11] phenyl-substituted ligands 1,2-bis(diphenylphosphino)ethane (entry 2, Table 1) and especially PPh_3 (entry 3, Table 1), electronic factors may prevail by virtue of their ability to significantly enhance the positive charge on the metal and the crotyl ligand.[12] As a result, a nucleophilic attack at the alkyl-substituted allyl terminus, where the positive charge is more stabilized, is favored.

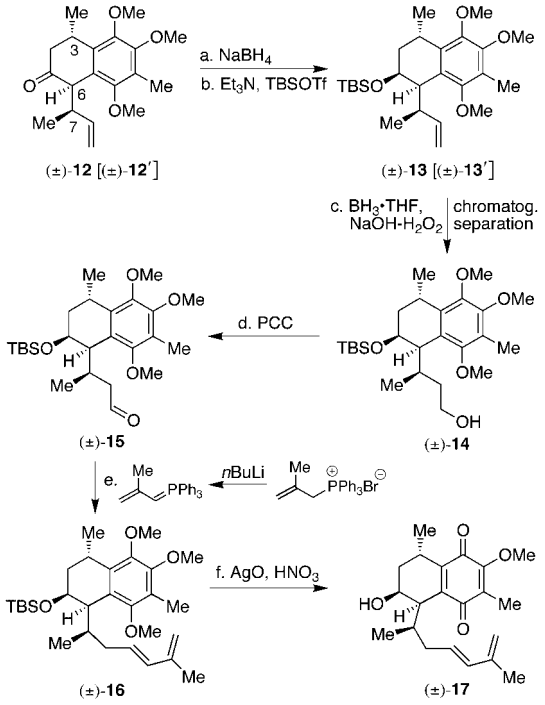
Table 1. Conditions and yields with different Pd catalysts, see Scheme 2.

	Conditions	Yield [%]	**12**:**12′**
1	[$Pd(OAc)_2$] (0.08 equiv), $P(OiPr)_3$ (0.5 equiv), THF, 25 °C, 30 min	74	1:4
2	[$Pd(dba)_3$]·$CHCl_3$ (0.05 equiv), DME, ($Ph_2PCH_2)_2$ (0.3 equiv), 25 °C, 80 h	78	1:1
3	[$Pd(PPh_3)_4$] (0.04 equiv), THF, 25 °C, 15 min	88	2.4:1

DME = Dimethoxyethane; dba = *trans*,*trans*-dibenzylideneacetone.

Although both regioisomers of the alkylated product [(±)-**12** and (±)-**12′**] were formed as single diastereoisomers, it was difficult at this stage to assign their relative stereochemistry. It was decided, however, to push forward with the construction of the diene side chain, hoping for full structural elucidation upon rigidification of the structure through the anticipated second [4+2] cycloaddition. Towards this end, the inseparable mixture of (±)-**12** and (±)-**12′** was stereoselectively reduced with $NaBH_4$ (96% yield), and the resulting secondary alcohols were protected as TBS ethers (TBSOTf/Et_3N, (±)-**13** and (±)-**13′**, 95% combined yield). The stereoselectivity observed in the reduction of those ketones is apparently totally controlled by the bulkiness of the C_6 substituent (Scheme 3). Hydroboration–oxidation (BH_3·THF, NaOH/H_2O_2, 82% combined yield) of the resulting mixture of olefins (±)-**13** and (±)-**13′** afforded a separable mixture of the primary alcohol (±)-**14** [derived from (±)-**13**] and a set of secondary alcohols [derived from (±)-**13′**]. The pure desired alcohol (±)-**14** was then oxidized by PCC to the corresponding aldehyde (±)-**15** (91% yield). Wittig olefination of the latter compound with the ylide derived from 2-methyl-2-propenyltriphenylphosphonium bromide and *n*BuLi then led to diene (±)-**16** as a mixture of two geometrical isomers (*E*:*Z* ca. 3:1). It is interesting to note that, although the aldehyde was rapidly consumed in this Wittig reaction (< 30 min, 25 °C), it was not until the reaction mixture was heated at 70 °C for 8 h that the 93% yield was realized; this suggests the formation of a stable betaine as an intermediate.

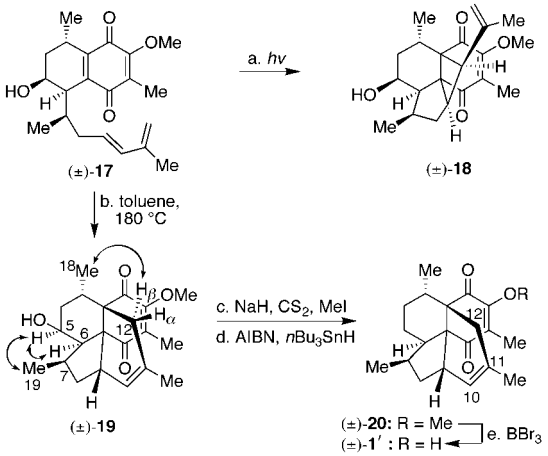
With the side chain installed, the stage was now set to unveil the quinone moiety in order to attempt the completion of the colombiasin skeleton and to ascertain the stereochemistry at C_6 and C_7. Several initial attempts for the demethylation ($AlBr_3$/EtSH) and the oxidative demethylation (e.g. ammonium cerium(IV) nitrate; $K_2S_2O_8$) of the trimethoxy aromatic ring failed. Finally, it was found that when a solution of (±)-**16**



Scheme 3. Construction of intramolecular Diels–Alder precursor (±)-**17**. a) $NaBH_4$ (3.0 equiv), MeOH, 25 °C, 30 min, 96%; b) Et_3N (2.0 equiv), TBSOTf (1.2 equiv), CH_2Cl_2, −78 °C, 1 h, 95%; c) BH_3•THF (3.0 equiv), THF, 25 °C, 2 h; then 3 M NaOH and 30% H_2O_2, 25 °C, 1 h, 82%; d) PCC (1.5 equiv), CH_2Cl_2, 25 °C, 1.5 h, 91%; e) 2-methyl-2-propenyltriphenylphosphonium bromide (1.5 equiv), *n*BuLi (1.5 equiv), THF, 0 → 25 °C, 1 h; then aldehyde (±)-**15**, 70 °C, 8 h, 70% plus 23% *Z* isomer; f) 1,4-dioxane/6 M HNO_3 10:1, 25 °C, 2 h; then AgO (5.0 equiv), 25 °C, 1 h, 27%. PCC = pyridinium chlorochromate.

in 1,4-dioxane was treated with AgO/HNO_3[6] at ambient temperature the coveted quinone (±)-**17** was obtained, albeit in only 27% isolated yield (Scheme 3). From the numerous unidentified by-products formed in this reaction, it was evident that the diene system was interfering, presumably due to the strong acidic conditions employed. Despite the low yield in this step, however, we were encouraged to go forward since we hoped to be able, at least then, to determine the pending stereochemical issues of our intermediates.

Scheme 4 displays the final stages of this endeavor. Strikingly, our initial attempts to thermally induce the desired intramolecular [4+2] cycloaddition within structure (±)-**17** (sealed tube, toluene, 120 °C, 12 h, ordinary room light) resulted in the exclusive formation of the [2 + 2]-cycloadduct (±)-**18** in 80% yield. Irradiation of (±)-**17** with visible light (sunlamp) in benzene at ambient temperature induced the same reaction, furnishing within 15 min a 91% yield of the [2 + 2]-product (±)-**18** (Scheme 4). This acceleration confirmed our suspicion that a photochemically-induced [2 + 2] cycloaddition was responsible for the conversion of (±)-**17** to (±)-**18**. All attempts to catalytically induce the desired intramolecular [4+2] cycloaddition (e.g. $BF_3 \cdot Et_2O$; $EtAlCl_2$) of (±)-**17** failed, leading to decomposition instead. To our delight, however, when (±)-**17** was heated in toluene solution at 180 °C in a sealed tube in the dark, the desired [4+2]-cycloadduct (±)-**19** was obtained in 89% yield (*endo*:*exo* ratio ca. 9:1). The ^1H NMR spectrum of this cycloadduct [(±)-**19**] was similar to that of the natural product **1**,[1] except for the chemical shift of Me_{19} (δ 1.18 for (±)-**19** versus δ 0.81 for colombiasin A). This difference was indicative of the wrong stereochemistry at C_7. Further proof for this assignment was the observed NOE between Me_{19} and H_5. The correct stereochemistry at C_6 was confirmed by observed NOEs for Me_{19}/H_5 and H_5/H_6 and the absence of a NOE between Me_{19} and H_6 [see arrows in structure (±)-**19**, Scheme 4]. The observed NOE between Me_{18} and $H_{12\beta}$ confirmed the desired relative stereochemistry at C_3.



Scheme 4. Synthesis of racemic 7-*epi*-colombiasin A [(±)-**1′**]. a) Visible light, benzene, 25 °C, 15 min, 91%; b) toluene (sealed tube), in dark, 180 °C, 5 h, 89%, *endo*:*exo* ca. 9:1; c) NaH (5.0 equiv), THF/CS_2/MeI 4:1:1, 50 °C, 5 h, 85%; d) AIBN (cat.), nBu_3SnH (5.0 equiv), toluene, careful deoxygenation, 110 °C, 30 min, 88%; e) BBr_3 (10 equiv), CH_2Cl_2, −78 °C, 20 min, 40%, plus 20% of $\Delta^{11,12}$-isomer (±)-**1″**. AIBN = 2,2′-azobisisobutyronitrile.

Having assembled the entire tetracyclic framework of colombiasin A in intermediate (±)-**19**, and despite the incorrect stereochemistry at C_7, we decided to continue our drive towards 7-*epi*-colombiasin A [(±)-**1′**] with at least three objectives in mind: first, to verify beyond any shadow of doubt the incorrect stereochemistry at C_7, second, to render the final target available for biological evaluation, and third, to prepare the ground for the arrival of the correct C_7 epimer and its final conversion to the natural product.

The short path remaining before arrival at 7-*epi*-colombiasin A [(±)-**1′**] required deoxygenation at C_5 and cleavage of the C_{16} methyl ether. In order to fulfill the first requirement, alcohol (±)-**19** was converted, in 85% yield, to the corresponding xanthate ester[13] by exposure to $NaH/CS_2/MeI$. Efforts to convert the sterically hindered hydroxy group in (±)-**19** to the corresponding thionoimidazolide or other activated esters for deoxygenation were unsuccessful. Treatment of the xanthate ester with nBu_3SnH and catalytic amounts of AIBN as radical initiator (Barton deoxygenation)[14] in toluene at 110 °C gave rise to racemic *O*-methyl 7-*epi*-colombiasin A [(±)-**20**]. The performance of this reductive cleavage varied, reaching 88% yield on relatively small scale (10 mg or less). The last task of the synthesis, namely the cleavage of the C_{16} methyl ether, also proved capricious. Thus, treatment of (±)-**20** with excess of BCl_3 or $AlCl_3$ (CH_2Cl_2, $-20 \rightarrow 0$ °C) resulted in decomposition of the starting materi-

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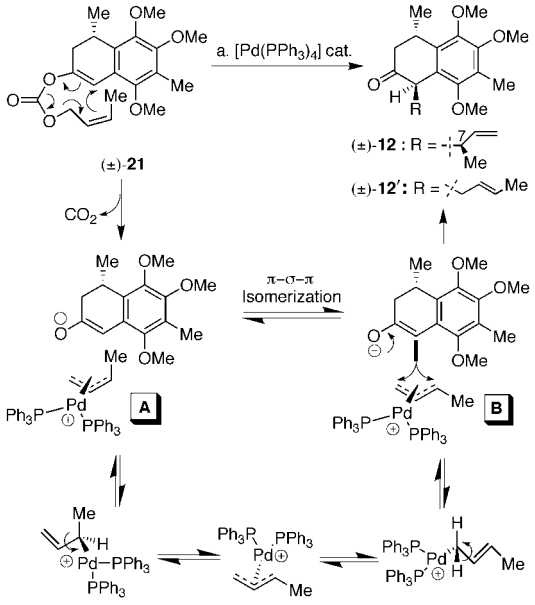
al, whereas $HClO_4$ (CH_2Cl_2, 25 °C) gave no demethylation, but migration of the double bond from the C_{10}–C_{11} to the C_{11}–C_{12} position. Finally, success was achieved by exposure of (±)-**20** to BBr_3 in CH_2Cl_2 at −78 °C (40% yield). A second demethylated product [(±)-**1″**], in which the C_{10}–C_{11} double bond was shifted to the adjacent C_{11}–C_{12} position, was also observed in this reaction in 20% yield. Having traversed the entire synthetic route to 7-*epi*-colombiasin A [(±)-**1′**] we felt obliged to return to the main task at hand, that of accomplishing the total synthesis of colombiasin A itself.

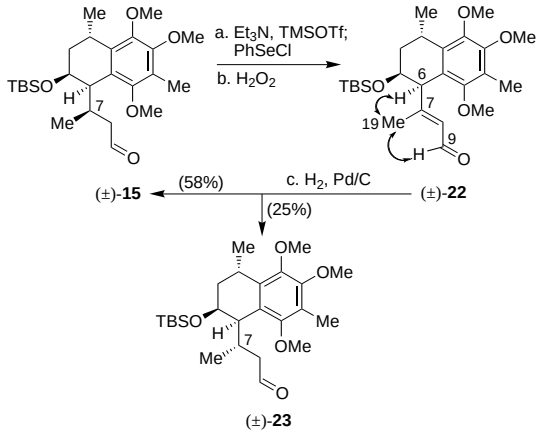
Second generation approach towards colombiasin A—Arrival at racemic colombiasin A: Our new plan to reach racemic colombiasin A [(±)-**1**] focused on the inversion of the stereochemistry at C_7. We first attempted to establish the desired stereochemistry at C_7 by utilizing the isomeric (*Z*)-crotyl enol carbonate (±)-**21** [prepared in a similar fashion to (±)-**4**] in the intramolecular Pd-catalyzed allylic alkylation (Scheme 5). To our disappointment, the same products (±)-**12** and (±)-**12′** were obtained in exactly the same ratio (ca. 2.4:1) upon treatment of (±)-**21** with catalytic amounts of [$Pd(PPh_3)_4$], giving further evidence that the reaction proceeds through the same reactive intermediates (see above) regardless of the geometry of the starting enol carbonate. A reasonable mechanistic explanation for this observation is outlined in Scheme 5. The *anti*-configured η^3-crotyl Pd-complex **A**, which



Scheme 5. Mechanistic rationale for the stereochemical outcome of the Pd-catalyzed allylic alkylation of the enol carbonate (±)-**21**.

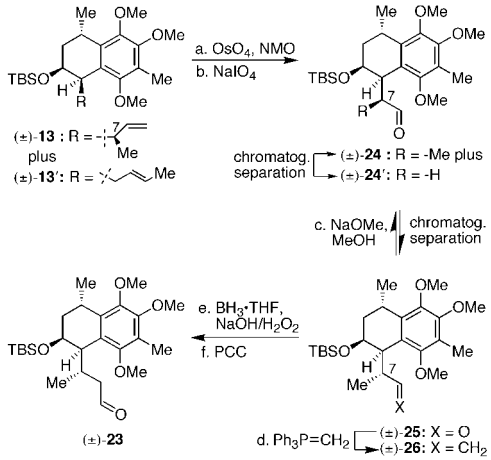
is initially formed from the (*Z*)-crotyl enol carbonate and which would lead to the desired stereochemistry at C_7 upon nucleophilic attack by the enolate, is rapidly equilibrated in a π–σ–π isomerization[15] to form the sterically more favored *syn*-configured complex **B**. Since a single isomer at C_6 and C_7 is formed in this reaction, despite the equimolar presence of both enantiomeric forms of the *syn*-η^3-crotyl Pd-complex **B** in this equilibrium, the chiral enolate nucleophile must discriminate between the two enantiotopic faces of the reactive species.

Having failed to establish the desired stereochemistry at C_7 by altering the geometry of the double bond in the precursor of the intramolecular Pd-catalyzed allylation, we turned our attention to an inversion tactic as a means for correcting the C_7 stereochemistry. Thus, we returned to aldehyde (±)-**15** as a precursor for such an attempt. Generation of the silylenol ether (TMSOTf/Et_3N) followed by addition of PhSeCl and oxidation–*syn*-elimination (H_2O_2) of the resulting α-phenylselenide, resulted in the formation of α,β-unsaturated aldehyde (±)-**22** in a moderate overall yield (30%). This procedure provided exclusively the *E* isomer of the α,β-unsaturated aldehyde (±)-**22**, as determined by compelling NOEs [see arrows in structure (±)-**22**, Scheme 6]. Regeneration of the C_7 stereocenter by catalytic hydrogenation of the



Scheme 6. First attempted epimerization of C_7. Arrival at the desired aldehyde (±)-**23**. a) Et_3N (2.0 equiv), TMSOTf (1.3 equiv), CH_2Cl_2, −78 °C, 3 h; then PhSeCl (1.3 equiv), −78 → 0 °C, 2 h, 38%; b) 30% H_2O_2 (excess), THF, 45 °C, 30 min, 78%; c) H_2, 10% Pd/C, EtOH, 25 °C, 4 h, 83%. TMS = trimethylsilyl.

α,β-unsaturated aldehyde (±)-**22** resulted in the formation of a mixture of the starting aldehyde (±)-**15** and the desired epimer (±)-**23** in a ratio of 7:3 in 83% total yield. This discouraging ratio, together with the relatively low yield of the preceding sequence (introduction of the double bond), led us to abandon this path in favor of a new one involving a shorter homologue of the aldehyde. This was accomplished by a two-step oxidative cleavage (OsO_4/NMO; $NaIO_4$)[16] of the terminal olefin (±)-**13** [which is contaminated with its isomer, disubstituted olefin (±)-**13′**, see above] to a chromatographically separable mixture of aldehyde (±)-**24** and its 7-demethyl analogue (±)-**24′** (Scheme 7). Treatment of aldehyde (±)-**24** with NaOMe in MeOH/THF resulted in an equilibrium mixture containing the starting (±)-**24** and the epimerized aldehyde (±)-**25** in a thermodynamically controlled ratio (±)-**24**:(±)-**25** of 2:1. After chromatographic separation of the two epimers, the correct isomer (±)-**25** could be olefinated to the terminal olefin, which has the desired stereochemistry at C_7, (±)-**26** ($Ph_3P{=}CH_2$, 97% yield) while the wrong isomer (±)-**24** was recycled to afford further quantities of (±)-**25**. Olefin (±)-**26** was then converted to aldehyde (±)-**23** (Scheme 7) by

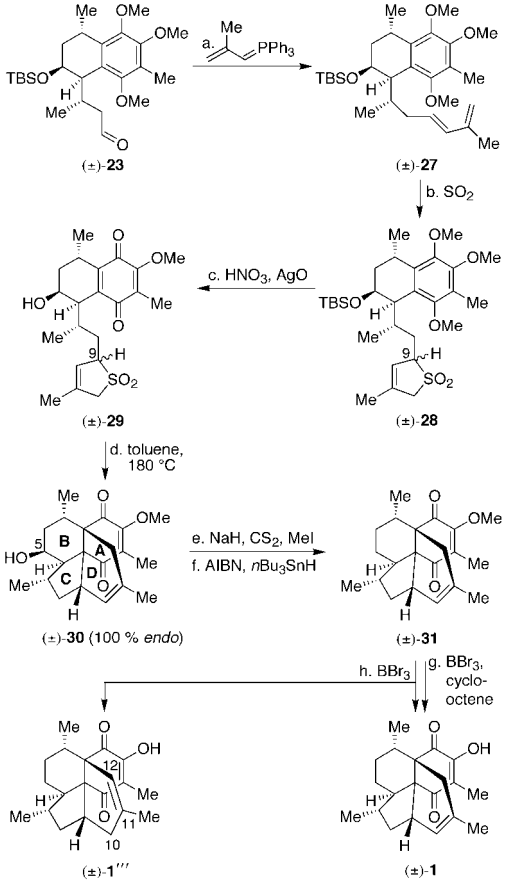


Scheme 7. Epimerization at C_7 and preparation of the desired pure aldehyde (±)-**23**. a) OsO_4 (0.04 equiv), NMO (2.0 equiv), acetone/H_2O 10:1, 25 °C, 5 h; b) $NaIO_4$ on silica gel, CH_2Cl_2, 25 °C, 30 min, 71% over two steps; c) NaOMe (4.0 equiv), MeOH/THF 2:1, 25 °C, 12 h, 50% of (±)-**25** and 45% of (±)-**24** after two cycles; d) methyltriphenylphosphonium bromide (1.5 equiv), KO*t*Bu (1.4 equiv), THF, 25 °C, 1 h; then (±)-**25**, 25 °C, 30 min, 97%; e) BH_3•THF (3.0 equiv), THF, 25 °C, 1 h; then 3 M NaOH and 30% H_2O_2, 25 °C, 1 h, 81%; f) PCC (1.5 equiv), CH_2Cl_2, 25 °C, 1 h, 97%. NMO = 4-methylmorpholine *N*-oxide.

the same hydroboration–oxidation procedure as described above for the C_7 epimeric compound. This aldehyde was then reacted with the conjugated phosphorane by the same procedure as before to afford the desired aromatic diene (±)-**27** in 97% yield (mixture of *E*:*Z* ca. 3:1, Scheme 8).

The oxidative demethylation of the aromatic ring of diene (±)-**27** was found to be more challenging than that of its epimer (±)-**16**. Only traces of the requisite diene-quinone were isolated under the same AgO/HNO_3 conditions employed to convert (±)-**27** to the corresponding quinone. As before, we suspected that the diene moiety was responsible for the failure (many unidentified by-products lacking the diene system were formed under the oxidative conditions), and thus decided to protect it as a cyclic sulfone[17] (Scheme 8). Thus, dissolution of (±)-**27** in liquid SO_2 in a sealed tube at ambient temperature led to clean formation of sulfone (±)-**28** (91% yield, ca. 1.3:1 mixture of C_9 epimers). Interestingly, and to our delight, the AgO/HNO_3 oxidative demethylation of these sulfones proceeded exceptionally well, furnishing a chromatographically separable mixture of two diastereomeric yellow quinones [(±)-**29**, ca. 1.3:1 ratio of C_9 epimers, 79% total yield]. Furthermore, when the individual quinone-sulfones [(±)-**29**] or a mixture of both were heated at 180 °C in the dark for 20 min, the same *endo* adduct (±)-**30** was exclusively obtained in 89% yield (Scheme 8). It was assumed that, upon cheletropic extrusion of SO_2, both sulfones gave the same diene system (*E* geometry) which then led to a single product as observed. The postulated stereoselective formation of the (*E*)-diene system was confirmed by subjecting the mixture of aromatic sulfones (±)-**28** to the above thermal conditions and observing the exclusive formation of the corresponding (*E*)-diene system after extrusion of SO_2.

With intermediate (±)-**30** in hand, arrival at colombiasin A was considered imminent. Deoxygenation at C_5 by the two-step protocol already described for the 7-*epi*-colombiasin A



Scheme 8. Completion of the synthesis of (±)-colombiasin A [(±)-**1**]. a) 2-methyl-2-propenyltriphenylphosphonium bromide (1.5 equiv), *n*BuLi (1.5 equiv), THF, 0 °C → 25 °C, 1 h; then aldehyde (±)-**23**, 70 °C, 8 h, 97% (*E*:*Z* = 3:1); b) SO_2, sealed tube, 25 °C, 30 min, 91%; c) 1,4-dioxane/6 N HNO_3 10:1, 25 °C, 2 h; then AgO (6.0 equiv), 25 °C, 1 h, 79%; d) toluene (sealed tube), 180 °C, 20 min, 89%; e) NaH (5.0 equiv), THF/CS_2/MeI 4:1:1, 50 °C, 3 h, 95%; f) AIBN (cat.), *n*Bu_3SnH (5.0 equiv), toluene, careful deoxygenation, 110 °C, 30 min, 77%; g) BBr_3 (10 equiv), *cis*-cyclooctene (20 equiv), CH_2Cl_2, −78 °C, 30 min, 43% yield based on 70% conversion; h) BBr_3 (10 equiv), CH_2Cl_2, −78 °C, 20 min, 30%, plus 20% of $\Delta^{11,12}$-isomer (±)-**1'''**.

series led to *O*-methyl colombiasin A [(±)-**31**], whose relationship to the natural product was clearly apparent upon spectroscopic comparisons. In an attempt to improve the final deprotection step, (±)-**31** was exposed to BBr_3 in the presence of excess of *cis*-cyclooctene as a competitive olefin, in order to suppress the previously observed, acid-induced migration of the double bond. Indeed, under these conditions, only colombiasin A [(±)-**1**] was formed after 30 min at −78 °C (43% yield based on 70% conversion). Under the original conditions (BBr_3, CH_2Cl_2, −78 °C), the $\Delta^{11,12}$-isomer (±)-**1'''** of colombiasin A was formed in 20% yield in addition to colombiasin A itself [(±)-**1**, 30%]. Synthetic colombiasin A [(±)-**1**] was identical with natural colombiasin A[18] (except for the lack of optical rotation) by the usual criteria (TLC, IR, ^1H and ^{13}C NMR, HRMS).

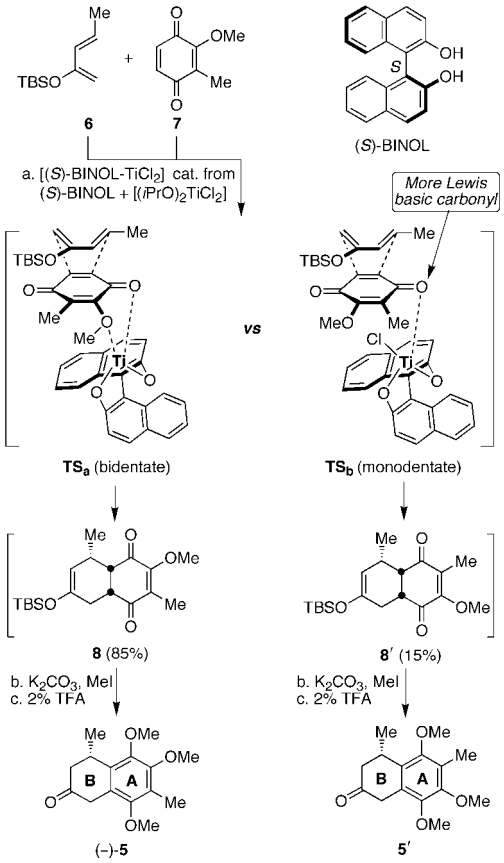
Third-generation approach towards colombiasin A—Arrival at natural colombiasin A and assignment of absolute configuration: With an expedient route to (±)-colombiasin A [(±)-**1**], at hand the stage was now set for the development of an

0947-6539/01/0724-5364 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 24

enantioselective total synthesis of this natural product and, hopefully, the determination of its absolute configuration. While induction of asymmetry in the first step (the intermolecular Diels–Alder reaction between **6** and **7**) would, in principle, suffice to achieve an asymmetric synthesis, accomplishment of the second objective would require the preparation of a suitable crystalline derivative absolute configuration which could be discernable from X-ray crystallographic analysis.

Scheme 9 summarizes the asymmetric construction of the first chiral building block of the colombiasin A sequence, compound (−)-**5**. Thus, in order to fix the C_3 stereocenter, the Diels–Alder cycloaddition of partners **6** and **7** was performed in toluene at $-60 \rightarrow -10\,^{\circ}C$ in the presence of the Mikami catalyst,[19] and 30 mol% [(*S*)-BINOL-$TiCl_2$], prepared[19b] from stoichiometric amounts of (*S*)-BINOL and [(*i*PrO)$_2$$TiCl_2$]. The Diels–Alder reaction afforded adduct **8** together with its undesired regioisomer **8′**. This mixture of the rather labile [4+2] cycloadducts (**8**+**8′**, ca. 85:15 ratio) was further elaborated according to the previously described procedure (i.e., aromatization–methylation–desilylation, see above) to afford a mixture of regioisomeric ketones [(−)-**5** and **5′**] in 70% overall yield for the three steps. Pure (−)-**5** was obtained by preparative TLC and its analysis by HPLC ($\tau_r = 6.1$ and 6.7 min for the two enantiomers, $0 \rightarrow 50\%$ *i*PrOH in hexane over 35 min, 1.5 mL min^{-1}, Daicel CHIRALCEL OD-H chiral column) revealed 94% *ee* ($[\alpha]_D^{25} = -140.0$, $c = 1.0$ in $CHCl_3$). The same asymmetric induction was also demonstrated in the opposite sense in the presence of the enantiomeric Mikami catalyst [(*R*)-BINOL-$TiCl_2$] under the same conditions. To rationalize the observed regio- and stereoselectivity of this catalytically induced asymmetric Diels–Alder cycloaddition, the transition states $\mathbf{TS_a}$ and $\mathbf{TS_b}$ (Scheme 9) are invoked. Thus, in transition state $\mathbf{TS_b}$ (leading to the minor regioisomer **8′**) the Lewis acid catalyst would normally be expected to coordinate to the vinylogous ester carbonyl oxygen due to the latter's higher Lewis basicity as compared to the other carbonyl oxygen. However, in this instance the coordination of the catalyst to the less Lewis basic carbonyl oxygen is apparently preferred due to the presence of the adjacent methoxy group which allows a bidentate arrangement as shown in $\mathbf{TS_a}$ (Scheme 9). This favorable bidentate coordination in the transition state explains the observed 85:15 regioselectivity of the reaction favoring the desired regioisomer **8**. Based on the same model,[19c] only the top face of the reactive double bond of the quinone is exposed for *endo* cycloaddition with the diene (see $\mathbf{TS_a}$), providing an explanation for the observed high asymmetric induction (94% *ee*) in this process. Attempts to minimize the formation of the undesired regioisomer (**8′**) by carrying out the reaction using less catalyst led to a dramatic loss in the enantiomeric induction. Thus the use of 5 mol% catalyst led to the exclusive formation of the desired regioisomer (−)-**5** but only in 15% *ee*, making this proposition impractical.

Although the proposed transition state model (Scheme 9) may be used to predict[19] the chirality of the product, it was considered prudent to confirm such a prediction by other means. To this end, a suitable crystalline derivative was sought



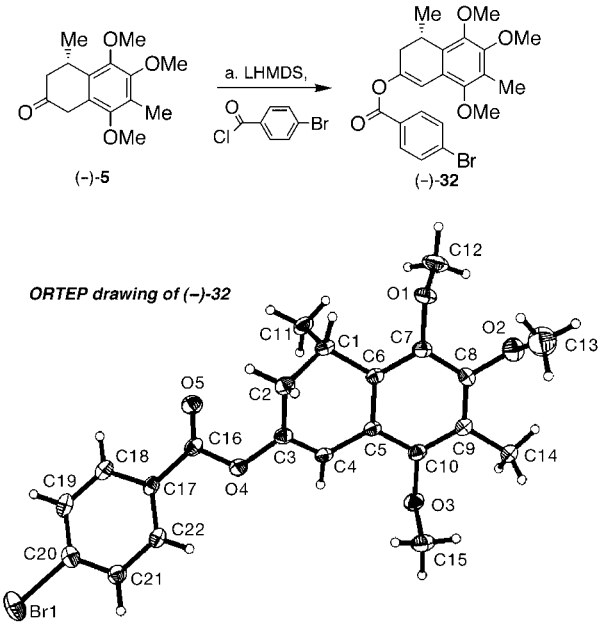
Scheme 9. Asymmetric construction of building block (−)-**5**. a) 30 mol% [(*S*)-BINOL-$TiCl_2$], toluene, $-60 \rightarrow -10\,^{\circ}C$, 7 h; b) K_2CO_3 (5.0 equiv), MeI (20 equiv), acetone, reflux, 48 h; c) 2% TFA in CH_2Cl_2, 25 °C, 2 h, 70% over three steps, 94% *ee*.

and found in the enol bromobenzoate (−)-**32** (Scheme 10) which was readily prepared from (−)-**5**. Thus, regioselective enolization (LHMDS) followed by acylation (4-bromobenzoyl chloride) afforded the desired enol bromobenzoate (−)-**32** (82% yield). The latter compound crystallized from pentane in enantiomerically pure form, forming colorless, monoclinic, parallelepiped-shaped crystals (m.p. 96–97 °C, from pentane). X-Ray crystallographic analysis of (−)-**32** confirmed the expected (*S*) absolute configuration at C_3 as shown in the exhibited ORTEP drawing (see Scheme 10).

All that remained before declaring the absolute stereochemistry of colombiasin A was to carry intermediate (−)-**5** through the previously charted sequence and compare the optical rotation of synthetic colombiasin A with that of the naturally derived substance. This task was done, resulting in the assignment of the shown 1*S*,2*S*,3*S*,6*R*,7*S*,9*S* absolute configuration of (−)-colombiasin A [synthetic: $[\alpha]_D^{25} = -61.0$ ($c = 0.1$, $CHCl_3$); natural: $[\alpha]_D^{25} = -55.3$ ($c = 0.9$, $CHCl_3$)]. Both the asymmetric total synthesis of colombiasin A and the assignment of its absolute configuration were thus achieved.

Conclusion

The described chemistry resulted in a flexible and expedient total synthesis of colombiasin A (**1**), reaching either the



Scheme 10. Preparation and ORTEP drawing of crystalline derivative (−)-**32**. a) LHMDS (1.2 equiv), THF, −78 °C, 1 h; then 4-bromobenzoyl chloride (1.4 equiv), −78 → 25 °C, 30 min, 82 %.

racemic or the naturally occurring form of the natural product and allowing assignment of its absolute configuration. In addition to providing laboratory access to this scarce marine natural product, this chemical synthesis allows the construction of a variety of analogues for possible chemical biology studies. Most significantly, these studies add considerably to our knowledge of the scope and generality of the Diels–Alder reaction as a means of complex molecule construction and enhance our ability to exploit it for asymmetric synthesis purposes.

Experimental Section

General techniques: Dry solvents were obtained by passing commercially available, pre-dried, oxygen-free formulations through activated alumina columns. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Irradiation experiments were performed with a sunlamp (300 W). Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel glass plates (60F-254) using UV light as visualizing agent and an acidic mixture of phosphomolybdic acid/cerium(IV) sulfate as developing agent. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 0.25, 0.50, or 1 mm E. Merck silica gel plates (60F-254).

NMR spectra were recorded on Bruker DRX-500 and DRX-600 instruments and calibrated by using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, sext = sextet, m = multiplet, br = broad. IR spectra were recorded on a Perkin–Elmer 1600 series FT-IR spectrometer and are presented as: s (strong), m (medium), w (weak), and br (broad). Electrospray ionization mass spectrometry (ESIMS) experiments were performed on an API 100 Perkin–Elmer SCIEX single quadrupole mass spectrometer at 4000 V emitter voltage. High resolution mass spectra (HRMS) were recorded on a VG ZAB-ZSE mass spectrometer under MALDI (matrix assisted laser desorption/ionization) conditions with DHB as the matrix. Melting points (m.p.) are uncorrected and were recorded on a Thomas–Hoover Unimelt capillary melting point apparatus.

Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-165225. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

[(*S*)-BINOL-TiCl$_2$]-Catalyzed and thermal intermolecular Diels–Alder reaction: Under an argon atmosphere, 2-methoxy-3-methyl-*p*-quinone[5, 6] (**7**, 4.10 g, 27.0 mmol) and [(*S*)-BINOL-TiCl$_2$][19b] (3.32 g, 8.2 mmol, 30 mol %) were dissolved in anhydrous toluene (40 mL). The deep red solution was cooled to −60 °C and a solution of (*E*)-2-(dimethyl-*tert*-butylsilyloxy)penta-1,3-diene (**6**, 6.43 g, 32.0 mmol, 1.2 equiv) in anhydrous toluene (17 mL) was added dropwise via syringe. The reaction mixture was stirred for 2 h and then warmed to −10 °C within ca. 2 h, the reaction progress being followed by TLC. Upon completion (essentially after 3 h at −10 °C), the solvent was removed in vacuo and the crude material was directly used for the following reaction in order to prevent loss of yield due to the instability of the Diels–Alder adduct.

The thermal Diels–Alder reaction between **6** and **7** was run in EtOH (50 mL, for the scale reported above), for 2 h at 25 °C. For NMR characterization of this [4+2] adduct a small sample was purified by flash column chromatography (silica gel, EtOAc/hexane 1:15) to give (±)-**8** as a slightly yellow oil. $R_f = 0.55$ (silica gel, EtOAc/hexane 1:2); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 4.84$ (d, $J = 4.8$ Hz, 1H), 3.96 (s, 3H), 3.16 (m, 2H), 2.66 (m, 2H), 2.13 (m, 1H), 1.92 (s, 3H), 0.91 (s, 9H), 0.89 (d, $J = 7.3$ Hz, 3H), 0.15 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 198.6$, 196.6, 159.7, 147.4, 133.2, 108.6, 59.9, 49.6, 45.9, 32.0, 27.0, 25.6, 19.2, 18.0, 9.6, −4.5, −4.6.

When (±)-**8** was purified by flash column chromatography, it was partially oxidized to the bicyclic quinone (±)-**9**, which was isolated as a yellow oil. $R_f = 0.62$ (silica gel, EtOAc/hexane 1:2); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta =$ 4.89 (m, 1H), 3.98 (s, 3H), 3.51 (m, 1H), 3.02 (m, 2H), 1.94 (s, 3H), 1.17 (d, $J = 7.0$ Hz, 3H), 0.93 (s, 9H), 0.16 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 187.9$, 182.6, 155.7, 146.3, 142.2, 138.3, 128.3, 106.8, 60.8, 30.5, 28.8, 25.6, 22.9, 18.0, 8.6, −4.5 (2C).

Aromatization–methylation and desilylation of Diels–Alder adduct 8—Formation of ketone (−)-5: Acetone (110 mL), powdered K_2CO_3 (18.60 g, 135 mmol), and iodomethane (76.70 g, 540 mmol) were added to the crude product of the asymmetric Diels–Alder reaction (**8**) and this reaction mixture was heated under reflux for 48 h. After cooling, the suspension was concentrated under vacuum and the residue was thoroughly extracted with hexane (100 mL). Insoluble Ti-compounds and excess K_2CO_3 were removed by filtration through a plug of celite. After removal of the solvent, the resulting slightly reddish oil was purified by flash column chromatography (silica gel, hexane → EtOAc/hexane 1:30) to give the corresponding homochiral aromatic silyl enol ether **11** (7.76 g, 76 % over two steps) as a slightly yellow oil. $R_f = 0.68$ (silica gel, EtOAc/hexane 1:2); IR (film): $\tilde{\nu}_{max} = 2933$ (m), 2859 (w), 1464 (m), 1411 (m), 1251 (m), 1202 (s), 1071 (m), 838 (s), 779 cm^{-1} (m); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 5.05$ (d, $J = 5.2$ Hz, 1H), 3.86 (s, 3H), 3.81 (s, 3H), 3.70 (s, 3H), 3.66 (m, 1H), 3.27 (m, 2H), 2.19 (s, 3H), 1.23 (d, $J = 6.6$ Hz, 3H), 0.97 (s, 9H), 0.20 (s, 3H), 0.18 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 151.5$, 149.9, 147.8, 146.8, 131.9, 123.3, 122.6, 108.0, 60.3, 59.9 (2C), 30.8, 29.0, 25.7, 24.1, 18.1, 9.3, −4.3, −4.4; HRMS (MALDI): calcd for $C_{21}H_{35}O_4Si$: 379.2299 $[M+H]^+$; found 379.2313.

The homochiral aromatic silyl enol ether **11** (7.76 g, 20.5 mmol) was dissolved in CH_2Cl_2 (50 mL) and a solution of trifluoroacetic acid (2.43 g, 21.3 mmol) in CH_2Cl_2 (40 mL) was slowly added at 25 °C. After stirring for 3 h, the reddish solution was washed with saturated, aqueous $NaHCO_3$ solution (3 × 50 mL) and dried over $MgSO_4$. The residue obtained after evaporation was purified by flash column chromatography (silica gel, EtOAc/hexane 1:8) to give ketone (−)-**5** (4.98 g, 92 %) as a pale-yellow solid. $R_f = 0.43$ (silica gel, EtOAc/hexane 1:2); $[\alpha]_D^{25} = -140.0$ ($c = 1.0$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 2954$ (m), 2360 (w), 1717 (s) (C=O), 1462 (s), 1409 (m), 1339 (m), 1295 (m), 1227 (w), 1111 (m), 1072 (s), 1008 (m), 963 cm^{-1} (w); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 3.88$ (s, 3H), 3.83 (s, 3H), 3.72 (m, 1H), 3.71 (d, $J = 22.0$ Hz, 1H), 3.67 (s, 3H), 3.35 (d, $J = 22.0$ Hz, 1H), 2.63 (dd, $J_1 = 15.2$ Hz, $J_2 = 5.9$ Hz, 1H), 2.51 (dd, $J_1 = 15.2$ Hz, $J_2 = 2.2$ Hz, 1H),

0947-6539/01/0724-5366 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 24

2.19 (s, 3H), 1.16 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta =$ 210.6, 152.0, 150.5, 146.3, 132.8, 123.8, 121.6, 60.8, 60.0 (2C), 46.1, 37.5, 28.7, 21.4, 9.3; HRMS (MALDI): calcd for $C_{15}H_{20}O_4$: 264.1362 $[M]^+$; found 264.1367.

HPLC analysis of (−)-**5** using a chiral column (Daicel CHIRALCEL OD-H, hexane → hexane/*i*PrOH 1:1 within 35 min, flow rate 1.5 mL min^{-1}, $\tau_r =$ 6.1 and 6.7 min for the two enantiomers) revealed 94% *ee*.

(*S*)-Enol bromobenzoate (−)-32: Under an argon atmosphere, a solution of LHMDS (1M in THF, 460 μL, 0.46 mmol, 1.2 equiv) was diluted with dry THF (3 mL). After cooling to −78 °C, enantiomerically pure ketone (−)-**5** (100 mg, 0.38 mmol), dissolved in dry THF (1 mL), was added dropwise and the resulting greenish reaction mixture was stirred for 1 h at this temperature. To this mixture was added a solution of 4-bromobenzoyl chloride (116 mg, 0.53 mmol, 1.4 equiv) in dry THF (2 mL) and the cooling bath was removed. After reaching room temperature and stirring for an additional 30 min, the reaction was quenched with saturated, aqueous NH_4Cl solution (5 mL), followed by extraction with Et_2O (2 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Purification of the crude product by flash column chromatography (silica gel, EtOAc/hexane 1:10) furnished enol ester (−)-**32** (139 mg, 82%) as a colorless glass. Upon treatment with pentane, colorless crystals formed. M.p. 96–97 °C (pentane); $R_f = 0.61$ (silica gel, EtOAc/hexane 1:2); $[\alpha]_D^{25} = -8.8$ ($c = 1.5$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 2935$ (m), 1734 (s) (C=O), 1589 (m), 1460 (m), 1405 (m), 1339 (m), 1312 (w), 1261 (s), 1144 (s), 1076 (s), 1010 (m), 966 (w), 750 cm^{-1} (m); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.99$ (d, $J =$ 8.6 Hz, 2H), 7.63 (d, $J = 8.6$ Hz, 2H), 6.54 (d, $J = 3.0$ Hz, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.69 (s, 3H), 3.47 (m, 1H), 2.99 (m, 1H), 2.22 (m, 1H), 2.18 (s, 3H), 1.24 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 164.2$, 150.9, 150.7, 149.1, 148.7, 146.3, 131.9 (2C), 131.5 (2C), 130.2, 128.6, 123.3, 120.9, 108.6, 61.3, 60.7, 60.1, 33.2, 27.7, 20.7, 9.2; HRMS (MALDI): calcd for $C_{22}H_{23}O_5Br$: 446.0723 $[M]^+$; found 446.0736.

***O*-Acylation of aromatic ketone (−)-5 to enol carbonate (−)-4**: A solution of LHMDS (1M in THF, 14.4 mL, 14.4 mmol, 1.2 equiv) was placed in a flask under an argon atmosphere and diluted with dry THF (140 mL). After cooling to −78 °C, ketone (−)-**5** (3.16 g, 12.0 mmol), dissolved in dry THF (45 mL), was added dropwise and the resulting greenish reaction mixture was stirred for 1 h at this temperature. In another flask, a solution of phosgene (1.9M in toluene, 11.1 mL, 21 mmol) was chilled to −35 °C and (*E*)-2-buten-1-ol (1.21 g, 16.8 mmol) was slowly added. After stirring for 30 min at −35 °C and 1 h at 0 °C, the excess of phosgene was removed by thoroughly bubbling argon through the solution at room temperature. The thus prepared (*E*)-2-buten-1-yl chloroformate reagent (ca. 1.3M in toluene, 16.8 mmol, 1.4 equiv) was added dropwise to the enolate solution (−78 °C) and the reaction mixture was allowed to reach ambient temperature. After stirring for 30 min, the reaction was quenched with saturated, aqueous NH_4Cl solution (100 mL), followed by extraction with Et_2O (2 × 150 mL). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo. Purification of the crude product by flash column chromatography (silica gel, EtOAc/hexane 1:10) furnished (−)-**4** (4.09 g, 94%) as a colorless syrup. $R_f = 0.57$ (silica gel, EtOAc/hexane 1:2); $[\alpha]_D^{25} = -16.1$ ($c = 2.7$, $CDCl_3$); IR (film): $\tilde{\nu}_{max} = 2937$ (w), 1756 (m) (C=O), 1457 (w), 1407 (w), 1231 (s), 1078 (m), 966 cm^{-1} (w); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 6.50$ (d, $J = 2.9$ Hz, 1H), 5.89 (m, 1H), 5.66 (m, 1H), 4.62 (d, $J = 6.6$ Hz, 2H), 3.86 (s, 3H), 3.81 (s, 3H), 3.67 (s, 3H), 3.43 (m, 1H), 2.88 (ddd, $J_1 = 16.9$ Hz, $J_2 = 7.3$ Hz, $J_3 =$ 2.9 Hz, 1H), 2.18 (m, 1H), 2.16 (s, 3H), 1.76 (dd, $J_1 = 6.6$ Hz, $J_2 = 0.7$ Hz, 3H), 1.18 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 152.9$, 150.9, 150.8, 148.4, 146.2, 132.8, 130.1, 124.2, 123.3, 120.9, 108.1, 69.0, 61.3, 60.7, 60.0, 32.7, 27.6, 20.6, 17.8, 9.1; HRMS (MALDI): calcd for $C_{20}H_{26}O_6Na$: 385.1621 $[M+Na]^+$; found 385.1612.

Intramolecular Pd-mediated allylic alkylation of enol carbonate (−)-4 to ketones 12 and 12′: Enol carbonate (−)-**4** (3.95 g, 10.9 mmol) was dissolved in dry THF (120 mL) under an argon atmosphere and $[Pd(PPh_3)_4]$ (0.50 g, 0.43 mmol, 4.0 mol%) was added at 25 °C. The mixture was stirred for 15 min and the solvent was evaporated. After purification of the residue by flash column chromatography (silica gel, EtOAc/hexane 1:10), a mixture of the α-allylated ketone **12** along with its regioisomer **12′** was isolated (total yield: 3.05 g, 88%, **12**:**12′** = 2.4:1) as a colorless oil. The analytical data for the desired regioisomer **12** are given: $R_f = 0.54$ (silica gel, EtOAc/hexane 1:2); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 5.53$ (ddd, $J_1 = 17.4$ Hz, $J_2 = 10.8$ Hz, $J_3 = 6.3$ Hz, 1H), 4.92 (dt, $J_1 = 10.8$ Hz, $J_2 = 1.7$ Hz, 1H), 4.81 (dt, $J_1 =$ 17.4 Hz, $J_2 = 1.7$ Hz, 1H), 3.88 (s, 3H), 3.82 (s, 3H), 3.68 (s, 3H), 3.50 (dd, $J_1 = 5.1$ Hz, $J_2 = 1.5$ Hz, 1H), 3.24 (m, 1H), 2.90 (dd, $J_1 = 12.8$ Hz, $J_2 =$ 7.0 Hz, 1H), 2.36 (m, 1H), 2.24 (d, $J = 12.8$ Hz, 1H), 2.19 (s, 3H), 1.14 (d, $J = 7.0$ Hz, 3H), 1.07 (d, $J = 7.4$ Hz, 3H); HRMS (MALDI): calcd for $C_{19}H_{27}O_4$: 319.1904 $[M+H]^+$; found 319.1897.

When the same procedure was applied to the isomeric (*Z*)-2-buten-1-yl enol carbonate (**21**), the same mixture of the α-allylated ketones **12** and **12′** was formed.

Reduction and silylation of the ketones 12 and 12′ to silyl ethers 13 and 13′: $NaBH_4$ (1.07 g, 28.2 mmol, 3.0 equiv) was added portionwise to a solution of the α-allylated ketones (3.00 g, 9.4 mmol, mixture of **12** and **12′**) in methanol (70 mL) and the reaction mixture was stirred for 30 min at room temperature. It was diluted with Et_2O (200 mL), washed with saturated aqueous $NaHCO_3$ solution (2 × 40 mL) and brine (40 mL), dried over $MgSO_4$, and concentrated to yield the crude alcohols (mixture of two regioisomers, total yield: 2.89 g, 96%).

To a solution of the crude regioisomeric alcohols (2.70 g, 8.4 mmol) in dry CH_2Cl_2 (90 mL) under argon at −78 °C was added triethylamine (1.70 g, 16.8 mmol, 2.0 equiv) and, subsequently, TBSOTf (2.67 g, 10.1 mmol, 1.2 equiv) dropwise. After stirring for 1 h, the cooling bath was removed and the reaction mixture was extracted with saturated aqueous $NaHCO_3$ solution (2 × 50 mL) and brine (40 mL), dried over $MgSO_4$, and concentrated. Purification of the residue by flash column chromatography (silica gel, EtOAc/hexane 1:20) furnished silyl ethers **13** and **13′** (mixture of regioisomers, total yield: 3.47 g, 95%) as a colorless oil. The analytical data for the major regioisomer **13** are given: $R_f = 0.70$ (silica gel, EtOAc/hexane 1:2); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 6.14$ (ddd, $J_1 = 17.4$ Hz, $J_2 = 10.6$ Hz, $J_3 = 7.7$ Hz, 1H), 4.90 (d, $J = 17.4$ Hz, 1H), 4.83 (d, $J = 10.6$ Hz, 1H), 4.25 (m, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.66 (s, 3H), 3.21 (m, 1H), 3.13 (m, 1H), 2.77 (m, 1H), 2.18 (s, 3H), 2.08 (m, 1H), 1.50 (m, 1H), 1.27 (d, $J = 7.0$ Hz, 3H), 0.94 (s, 9H), 0.56 (d, $J = 7.0$ Hz, 3H), 0.11 (s, 3H), 0.10 (s, 3H); GC/MS: calcd for $C_{25}H_{42}O_4Si$: 434 $[M]^+$; found 434.

Oxidative cleavage of terminal olefin 13 to 7-*epi*-aldehyde (−)-24: A mixture of the isomeric homochiral olefins **13** and **13′** (3.40 g, 7.8 mmol) was dissolved in a mixture of acetone/water 10:1 (200 mL) and 4-methylmorpholine *N*-oxide (1.83 g, 15.6 mmol, 2.0 equiv) and OsO_4 (2.5 wt.% solution in *t*BuOH, 3.9 mL, 4.0 mol%) were added subsequently. After stirring at room temperature for 5 h, the reaction mixture was diluted with EtOAc (200 mL) and washed with brine (3 × 50 mL). Drying over $MgSO_4$ and removal of the solvent afforded a mixture of crude diols.

A solution of the latter compounds (3.15 g, 6.8 mmol) in CH_2Cl_2 (30 mL) was added dropwise to a suspension of silica gel supported $NaIO_4$[16] (14.5 g) in CH_2Cl_2 (30 mL). The reaction mixture was stirred for 30 min at room temperature. After filtration and evaporation of the solvent, the resulting residue was carefully purified by flash column chromatography (silica gel, EtOAc/hexane 1:20) in order to separate aldehyde (−)-**24** (1.73 g, 51% over two steps) from its 7-demethyl isomer **24′** (0.66 g, 20% over two steps). Analytical data are given only for the requisite isomer (−)-**24**: colorless syrup. $R_f = 0.52$ (silica gel, EtOAc/hexane 1:2); $[\alpha]_D^{25} = -16.3$ ($c = 1.9$, $CDCl_3$); IR (film): $\tilde{\nu}_{max} = 2936$ (m), 1726 (m) (C=O), 1462 (m), 1405 (m), 1252 (w), 1109 (s), 1010 (w), 884 (m), 838 (s), 778 cm^{-1} (m); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 9.70$ (s, 1H), 4.32 (ddd, $J_1 = 8.8$ Hz, $J_2 =$ 5.3 Hz, $J_3 = 3.5$ Hz, 1H), 3.83 (s, 3H), 3.78 (s, 3H), 3.61 (s, 3H), 3.59 (m, 1H), 3.24 (m, 1H), 2.91 (qd, $J_1 = 7.4$ Hz, $J_2 = 3.0$ Hz, 1H), 2.14 (s, 3H), 1.90 (td, $J_1 = 12.9$ Hz, $J_2 = 6.4$ Hz, 1H), 1.59 (m, 1H), 1.29 (d, $J = 7.0$ Hz, 3H), 0.92 (s, 9H), 0.64 (d, $J = 7.4$ Hz, 3H), 0.14 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 205.2$, 152.6, 150.5, 147.5, 133.3, 124.8, 122.9, 67.0, 60.4, 59.9, 59.6, 43.8, 39.5, 35.5, 29.2, 25.9, 23.5, 18.2, 12.2, 9.5, −4.7 (2C); HRMS (MALDI): calcd for $C_{24}H_{40}O_5SiNa$: 459.2537 $[M+Na]^+$; found 459.2554.

Epimerization of 7-*epi*-aldehyde (−)-24 to the desired aldehyde (−)-25: NaOMe (0.75 g, 14.0 mmol, 4.0 equiv) was added to a solution of (−)-**24** (1.54 g, 3.5 mmol) in a MeOH/THF mixture 2:1 (60 mL) and the reaction mixture was stirred for 12 h. After Et_2O (100 mL) was added and the mixture was washed with water (2 × 40 mL) it was dried over $MgSO_4$. The solvent was removed and the resulting residue was carefully purified by flash column chromatography (silica gel, EtOAc/hexane 1:20) in order to separate aldehyde (−)-**25** (0.51 g, 33%) from unreacted (−)-**24** (0.98 g, 64%). The recovered starting material was employed in a second reaction cycle to furnish a second charge of (−)-**25** [yield after two cycles: 0.77 g, 50% of (−)-**25** plus 0.69 g, 45% of (−)-**24**]. (−)-**25**: colorless syrup.

$R_f = 0.50$ (silica gel, EtOAc/hexane 1:2); $[\alpha]_D^{25} = -10.5$ ($c = 1.0$, $CDCl_3$); IR (film): $\tilde{\nu}_{max} = 2935$ (s), 1723 (m) (C=O), 1461 (m), 1404 (m), 1331 (w), 1253 (m), 1105 (s), 1071 (s), 1009 (m), 880 (m), 837 (s), 777 cm^{-1} (m); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 9.50$ (d, $J = 1.1$ Hz, 1H), 4.31 (ddd, $J_1 = 9.9$ Hz, $J_2 = 6.2$ Hz, $J_3 = 4.0$ Hz, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 3.73 (s, 3H), 3.62 (br dd, $J_1 = 6.2$ Hz, $J_2 = 3.3$ Hz, 1H), 3.29 (m, 1H), 2.89 (qd, $J_1 = 7.0$ Hz, $J_2 = 3.1$ Hz, 1H), 2.16 (s, 3H), 2.11 (td, $J_1 = 12.9$ Hz, $J_2 = 6.2$ Hz, 1H), 1.60 (dd, $J_1 = 12.8$ Hz, $J_2 = 4.0$ Hz, 1H), 1.24 (d, $J = 7.0$ Hz, 3H), 1.10 (d, $J = 7.0$ Hz, 3H), 0.92 (s, 9H), 0.11 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 204.7$, 152.2, 150.5, 147.2, 133.6, 125.2, 123.5, 67.6, 60.4, 60.3, 59.9, 47.9, 42.1, 35.5, 29.1, 25.9, 23.4, 18.2, 13.6, 9.5, −4.5, −4.8; HRMS (MALDI): calcd for $C_{24}H_{40}O_5SiNa$: 459.2537 $[M+Na]^+$; found 459.2554.

Wittig olefination of the desired aldehyde (−)-25 to the terminal alkene (−)-26: A flask was charged with methyltriphenylphosphonium bromide (0.70 g, 2.0 mmol, 1.5 equiv) which was suspended in dry THF (10 mL) under an argon atmosphere. A solution of KO*t*Bu (1M in THF, 1.80 mL, 1.8 mmol, 1.4 equiv) was added dropwise at room temperature and the mixture was stirred for 1 h. Thereafter, a solution of the homochiral aldehyde (−)-**25** (0.57 g, 1.3 mmol) in dry THF (10 mL) was added dropwise. After stirring for 30 min at the same temperature, most of the solvent was removed in vacuo and the resulting material was purified by flash column chromatography (silica gel, EtOAc/hexane 1:20) to afford (−)-**26** (0.55 g, 97%) as a colorless oil. $R_f = 0.70$ (silica gel, EtOAc/hexane 1:2); $[\alpha]_D^{25} = -7.5$ ($c = 4.0$, $CDCl_3$); IR (film): $\tilde{\nu}_{max} = 2935$ (s), 1461 (m), 1405 (m), 1330 (w), 1252 (m), 1108 (s), 1010 (m), 965 (w), 887 (m), 838 (m), 776 cm^{-1} (m); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 5.20$ (m, 1H), 4.71 (dd, $J_1 = 16.9$ Hz, $J_2 = 2.2$ Hz, 1H), 4.50 (dd, $J_1 = 10.3$ Hz, $J_2 = 2.2$ Hz, 1H), 4.23 (m, 1H), 3.79 (s, 6H), 3.68 (s, 3H), 3.15 (m, 1H), 3.04 (m, 1H), 2.77 (m, 1H), 2.18 (s, 3H), 2.18 (m, 1H), 1.45 (m, 1H), 1.24 (d, $J = 7.0$ Hz, 3H), 1.25 (d, $J = 7.0$ Hz, 3H), 0.95 (s, 9H), 0.13 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 152.7$, 149.9, 147.4, 144.6, 132.9, 127.4, 122.6, 111.7, 68.3, 60.4, 60.0, 59.7, 46.0, 38.0, 34.5, 29.4, 26.0, 23.9, 23.5, 18.3, 9.5, −4.5, −4.6; GC/MS: calcd for $C_{25}H_{42}O_4Si$: 434 $[M]^+$; found 434.

Hydroboration–oxidation of the terminal alkene (−)-26 and subsequent PCC oxidation to aldehyde (+)-23: $BH_3 \cdot THF$ (1M in THF, 3.9 mL, 3.9 mmol, 3.0 equiv) was added to a solution of (−)-**26** (0.55 g, 1.3 mmol) in dry THF (15 mL) at room temperature and the mixture was stirred for 2 h. Thereafter, an aqueous solution of NaOH (3M, 3 mL) was slowly introduced into the flask and the mixture was stirred for 30 min, before aqueous H_2O_2 (30%, 3 mL) was added dropwise. After stirring for an additional 30 min, the reaction mixture was diluted with Et_2O (30 mL) and washed with water (2 × 20 mL) and brine (20 mL). The organic phase was dried over $MgSO_4$ and concentrated and the resulting residue was purified by flash column chromatography (silica gel, EtOAc/hexane 1:5) to yield the primary (−)-alcohol (0.48 g, 81%) as a colorless glass. $R_f = 0.19$ (silica gel, EtOAc/hexane 1:4); $[\alpha]_D^{25} = -8.8$ ($c = 1.7$, $CDCl_3$); IR (film): $\tilde{\nu}_{max} = 3425$ (br w) (OH), 2936 (s), 1461 (m), 1405 (m), 1329 (w), 1251 (m), 1106 (s), 1067 (s), 1011 (m), 886 (w), 837 (m), 776 cm^{-1} (w); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 4.23$ (ddd, $J_1 = 8.7$ Hz, $J_2 = 5.2$ Hz, $J_3 = 3.3$ Hz, 1H), 3.81 (s, 3H), 3.78 (s, 3H), 3.67 (s, 3H), 3.55 (m, 1H), 3.45 (m, 1H), 3.20 (m, 1H), 3.00 (m, 1H), 2.17 (s, 3H), 2.06 (m, 2H), 1.58 (br s, 1H), 1.48 (m, 1H), 1.25 (d, $J = 7.0$ Hz, 3H), 1.14 (d, $J = 7.0$ Hz, 3H), 1.06 (m, 2H), 0.93 (s, 9H), 0.11 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 152.6$, 149.9, 147.3, 133.1, 127.7, 122.8, 68.4, 61.8, 60.3, 59.8, 59.6, 45.0, 38.0, 34.9, 29.6, 29.4, 25.9, 23.6, 22.4, 18.2, 9.5, −4.6, −4.8; HRMS (MALDI): calcd for $C_{25}H_{44}O_5SiNa$: 475.2850 $[M+Na]^+$; found 475.2860.

To a solution of the intermediate primary (−)-alcohol (0.33 g, 0.73 mmol) in dry CH_2Cl_2 (15 mL) was added pyridinium chlorochromate (0.24 g, 1.11 mmol, 1.5 equiv) and the resulting mixture was stirred for 1 h. Then, celite was added until the reaction mixture became rather thick. This was directly purified by flash column chromatography (silica gel, EtOAc/hexane 1:10) to furnish aldehyde (+)-**23** (0.32 g, 97%) as a colorless syrup. $R_f = 0.43$ (silica gel, EtOAc/hexane 1:4); $[\alpha]_D^{25} = +1.6$ ($c = 3.2$, $CDCl_3$); IR (film): $\tilde{\nu}_{max} = 2935$ (m), 2360 (m), 1724 (m) (C=O), 1461 (m), 1405 (m), 1251 (m), 1106 (s), 1059 (s), 1012 (m), 838 (m), 776 cm^{-1} (m); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 9.31$ (t, $J = 2.2$ Hz, 1H), 4.25 (ddd, $J_1 = 8.7$ Hz, $J_2 = 5.2$ Hz, $J_3 = 3.3$ Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 3.67 (s, 3H), 3.17 (m, 1H), 2.97 (m, 1H), 2.63 (m, 1H), 2.18 (s, 3H), 2.08 (td, $J_1 = 12.8$ Hz, $J_2 = 6.6$ Hz, 1H), 1.88 (m, 2H), 1.53 (m, 1H), 1.25 (d, $J = 7.0$ Hz, 3H), 1.23 (d, $J = 7.0$ Hz, 3H), 0.95 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 203.7$, 152.6, 150.4, 147.6, 133.0, 127.2, 123.3, 68.0, 60.3, 59.9, 59.5, 49.3, 45.0, 34.7, 29.3, 28.6, 26.0, 23.8, 23.6, 18.3, 9.5, −4.6, −4.7; HRMS (MALDI): calcd for $C_{25}H_{42}O_5SiNa$: 473.2694 $[M+Na]^+$; found 473.2710.

The same procedure (hydroboration–oxidation, see above) was applied to convert the 7-*epi*-olefin (±)-**13** [mixture with the regioisomer (±)-**13′**] into the respective 7-*epi*-alcohol (±)-**14**. At this stage, the desired primary alcohol (±)-**14** could be separated and was obtained as a colorless glass. $R_f = 0.25$ (silica gel, EtOAc/hexane 1:4); IR (film): $\tilde{\nu}_{max} = 3442$ (br w) (OH), 2935 (s), 1461 (m), 1405 (m), 1329 (w), 1252 (m), 1108 (s), 1067 (s), 1010 (m), 882 (w), 837 (m), 777 cm^{-1} (w); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 4.23$ (m, 1H), 3.84–3.77 (m, 2H), 3.81 (s, 3H), 3.79 (s, 3H), 3.66 (s, 3H), 3.21 (m, 1H), 3.12 (m, 1H), 2.18 (s, 3H), 2.16 (m, 1H), 2.04 (td, $J_1 = 12.7$ Hz, $J_2 = 6.6$ Hz, 1H), 1.91 (m, 1H), 1.74 (sext, $J = 7.0$ Hz, 1H), 1.69 (br s, 1H), 1.53 (m, 1H), 1.28 (d, $J = 7.0$ Hz, 3H), 0.96 (s, 9H), 0.36 (d, $J = 7.4$ Hz, 3H), 0.16 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 152.8$, 150.0, 147.4, 133.0, 127.2, 122.6, 69.2, 61.0, 60.3, 59.9, 59.8, 42.6, 41.8, 34.6, 29.6, 27.5, 26.2, 23.8, 19.3, 18.5, 9.5, −4.2, −4.6; HRMS (MALDI): calcd for $C_{25}H_{44}O_5SiNa$: 475.2850 $[M+Na]^+$; found 475.2862.

The same procedure (PCC oxidation, see above) was applied to convert 7-*epi*-primary alcohol (±)-**14** into the respective 7-*epi*-aldehyde (±)-**15**: colorless syrup. $R_f = 0.44$ (silica gel, EtOAc/hexane 1:4); IR (film): $\tilde{\nu}_{max} = 2935$ (s), 2361 (m), 1723 (m) (C=O), 1461 (m), 1405 (m), 1252 (m), 1107 (s), 1067 (s), 1010 (m), 838 (m), 776 (m); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 9.76$ (t, $J = 2.6$ Hz, 1H), 4.22 (m, 1H), 3.81 (s, 3H), 3.78 (s, 3H), 3.64 (s, 3H), 3.21 (m, 1H), 2.95 (m, 1H), 2.71 (m, 2H), 2.58 (m, 1H), 2.17 (s, 3H), 2.03 (td, $J_1 = 12.7$ Hz, $J_2 = 6.6$ Hz, 1H), 1.52 (m, 1H), 1.26 (d, $J = 7.0$ Hz, 3H), 0.92 (s, 9H), 0.44 (d, $J = 7.0$ Hz, 3H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 204.3$, 152.9, 150.2, 147.5, 133.0, 126.5, 122.8, 68.2, 60.4, 59.9, 59.6, 53.6, 43.9, 34.7, 29.4, 26.7, 26.0, 23.7, 18.8, 18.2, 9.5, −4.5, −4.8; HRMS (MALDI): calcd for $C_{25}H_{42}O_5SiNa$: 473.2694 $[M+Na]^+$; found 473.2712.

***α,β*-Unsaturated aldehyde (±)-22**: A solution of the aldehyde (±)-**15** (50 mg, 0.11 mmol) in anhydrous CH_2Cl_2 (2 mL) was chilled to −78 °C under an argon atmosphere and Et_3N (22 mg, 0.22 mmol, 2.0 equiv) and TMSOTf (31 mg, 0.14 mmol, 1.3 equiv) were added. The reaction mixture was stirred for 3 h at this temperature, before a solution of PhSeCl (27 mg, 0.14 mmol, 1.3 equiv) in anhydrous CH_2Cl_2 (0.3 mL) was added dropwise. The reaction mixture was then allowed to warm to 0 °C and stirred for 2 h. After diluting with CH_2Cl_2 (5 mL) and washing with saturated aqueous $NaHCO_3$ solution (5 mL), the organic phase was dried ($MgSO_4$) and concentrated. The resulting residue was purified by flash column chromatography (silica gel, EtOAc/hexane 1:20) to afford the respective (±)-*α*-selenoaldehyde (25 mg, 38%).

The (±)-*α*-selenoaldehyde (18 mg, 30 μmol) was dissolved in THF (1 mL) and an excess of aqueous H_2O_2 solution (30%, ca. four drops) was added. This mixture was heated to 45 °C and stirred for 30 min. After cooling to room temperature, Et_2O (5 mL) was added and the mixture was washed with water (5 mL). The organic phase was dried ($MgSO_4$) and concentrated and the resulting residue was purified by flash column chromatography (silica gel, EtOAc/hexane 1:20) to give the *α,β*-unsaturated aldehyde (±)-**22** (10.5 mg, 78%) as a colorless syrup. $R_f = 0.44$ (silica gel, EtOAc/hexane 1:4); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 10.00$ (d, $J = 8.3$ Hz, 1H), 5.26 (d, $J = 8.3$ Hz, 1H), 4.39 (m, 1H), 3.93 (d, $J = 6.4$ Hz, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 3.64 (s, 3H), 3.25 (m, 1H), 2.46 (d, $J = 1.4$ Hz, 3H), 2.13 (s, 3H), 2.06 (m, 1H), 1.50 (m, 1H), 1.27 (d, $J = 6.9$ Hz, 3H), 0.93 (s, 9H), 0.15 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 191.3$, 168.3, 151.9, 150.9, 147.0, 133.1, 130.4, 125.9, 123.3, 68.0, 60.4, 60.1, 59.9, 49.6, 33.8, 29.3, 26.0, 23.0, 22.0, 18.3, 9.8, −4.5, −4.7. Assignment of the *E* geometry of the C=C double bond was aided by NOE experiments: irradiation of the signal at $\delta = 2.46$ (allylic CH_3) effects the signals at $\delta = 10.00$ (1.1%, -CHO) and 3.93 (0.7%).

Hydrogenation of the *α,β*-unsaturated aldehyde (±)-22 to aldehydes (±)-15 and (±)-23: Under an argon atmosphere, the racemic *α,β*-unsaturated aldehyde (±)-**22** (10 mg, 22 μmol) was dissolved in EtOH (2 mL) and Pd/C (10 wt.%, 4.6 mg, 20 mol% Pd) was added at room temperature. A hydrogen atmosphere was established in the reaction flask and the mixture was stirred for 4 h. Thereafter, the Pd catalyst was removed by filtration and the solvent was evaporated. Purification of the resulting residue by flash column chromatography (silica gel, EtOAc/hexane 1:20) yielded aldehydes (±)-**15** (5.8 mg, 58%) and (±)-**23** (2.5 mg, 25%). For analytical data of those compounds, see above.

0947-6539/01/0724-5368 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 24

Wittig olefination of aldehyde (+)-23 to homochiral diene 27: Under an argon atmosphere, *n*BuLi (1.6 M in hexane, 590 μL, 0.95 mmol, 1.5 equiv) was added to a suspension of 2-methyl-2-propenyltriphenylphosphonium bromide (378 mg, 0.95 mmol, 1.5 equiv) in dry THF (8 mL) at 0 °C. The reaction mixture was allowed to warm to ambient temperature and stirred for 1 h before a solution of aldehyde (+)-**23** (285 mg, 0.63 mmol) in dry THF (2 mL) was added dropwise. The mixture was then heated under reflux for 8 h. After cooling to room temperature, most of the solvent was evaporated and the resulting residue was purified by flash column chromatography (silica gel, EtOAc/hexane 1:20) to afford homochiral diene **27** (300 mg, 97 %) as a mixture of the *E* and *Z* isomer (*E*:*Z* = 3:1). Only the data of the major *E* isomer are given; colorless syrup. $R_f = 0.71$ (silica gel, EtOAc/hexane 1:2); IR (film): $\tilde{\nu}_{max} = 2933$ (s), 1460 (m), 1405 (m), 1251 (m), 1106 (s), 1067 (s), 1011 (m), 965 (m), 883 (m), 837 (m), 775 cm^{-1} (m); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 5.89$ (d, $J = 15.8$ Hz, 1H), 5.43 (m, 1H), 4.77 (s, 1H), 4.75 (s, 1H), 4.22 (m, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 3.68 (s, 3H), 3.19 (m, 1H), 3.01 (m, 1H), 2.19 (s, 3H), 2.18 (m, 1H), 2.05 (m, 2H), 1.76 (s, 3H), 1.51 (m, 2H), 1.28 (d, $J = 7.0$ Hz, 3H), 1.16 (d, $J = 7.0$ Hz, 3H), 0.95 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 163.1$, 152.8, 149.9, 147.4, 142.3, 133.0, 131.6, 127.7, 122.8, 113.5, 68.4, 60.4, 59.9, 59.5, 45.6, 38.5, 34.9, 32.9, 29.5, 26.0, 23.6, 23.0, 18.7, 18.3, 9.6, −4.5, −4.7; ESIMS ($C_{29}H_{48}O_4Si$): *m*/*z* (%): 511 (10) $[M+Na]^+$.

The same procedure was applied to convert 7-*epi*-aldehyde (±)-**15** into the respective 7-*epi*-diene (±)-**16**: colorless syrup. $R_f = 0.71$ (silica gel, EtOAc/hexane 1:2); IR (film): $\tilde{\nu}_{max} = 2927$ (s), 1460 (s), 1406 (m), 1252 (m), 1107 (s), 1073 (s), 1015 (m), 965 (w), 880 (m), 836 (m), 776 cm^{-1} (w); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.19$ (d, $J = 15.4$ Hz, 1H), 5.70 (dt, $J_1 = 15.4$ Hz, $J_2 = 7.5$ Hz, 1H), 4.85 (s, 1H), 4.84 (s, 1H), 4.22 (m, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.66 (s, 3H), 3.20 (m, 1H), 2.99 (m, 1H), 2.47 (m, 1H), 2.32 (m, 1H), 2.19 (s, 3H), 2.16 (m, 1H), 2.03 (td, $J_1 = 12.7$ Hz, $J_2 = 6.6$ Hz, 1H), 1.85 (s, 3H), 1.50 (m, 1H), 1.28 (d, $J = 7.0$ Hz, 3H), 0.96 (s, 9H), 0.34 (d, $J = 7.4$ Hz, 3H), 0.13 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 153.0$, 149.9, 147.4, 142.5, 133.5, 133.1, 131.2, 127.5, 122.6, 113.7, 68.3, 60.4, 59.9, 59.7, 44.3, 43.0, 34.8, 32.1, 29.5, 26.0, 23.9, 18.8, 18.3, 17.9, 9.5, −4.5, −4.8; ESIMS ($C_{29}H_{48}O_4Si$): *m*/*z* (%): 511 (10) $[M+Na]^+$.

Oxidative demethylation of aromatic diene (±)-16 to diene-quinone (±)-17: Aqueous HNO_3 (6 M, 100 μL, 0.6 mmol, 10 equiv) was added at room temperature to a solution of racemic aromatic diene (±)-**16** (30 mg, 0.06 mmol) in 1,4-dioxane (1 mL) and the mixture was stirred for 2 h. The flask was wrapped with aluminium foil (exclusion of light) before AgO (37 mg, 0.3 mmol, 5.0 equiv) was added portionwise. After stirring for 1 h, the red reaction mixture was diluted with Et_2O (5 mL) and washed with water (3 × 3 mL). The organic phase was dried ($MgSO_4$) and concentrated and the resulting red residue was purified by flash column chromatography (silica gel, EtOAc/hexane 1:15 → 1:4) to afford (±)-**17** (5.6 mg, 27 %) as a yellow glass. $R_f = 0.34$ (silica gel, EtOAc/hexane 1:2); IR (film): $\tilde{\nu}_{max} = 3490$ (w) (OH), 2956 (m), 2360 (s), 1645 (m) (C=O), 1478 (m), 1345 (m), 1142 cm^{-1} (m); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.29$ (d, $J = 15.8$ Hz, 1H), 5.71 (dt, $J_1 = 15.8$ Hz, $J_2 = 7.7$ Hz, 1H), 4.91 (s, 2H), 4.04 (br m, 1H), 3.99 (s, 3H), 3.11 (m, 2H), 2.61 (m, 1H), 2.44 (m, 1H), 2.22 (m, 1H), 2.08 (m, 1H), 1.96 (s, 3H), 1.59 (m, 1H), 1.54 (s, 3H), 1.19 (d, $J = 7.0$ Hz, 3H), 0.64 (d, $J = 7.0$ Hz, 3H); HRMS (MALDI): calcd for $C_{21}H_{29}O_4$: 345.2060 $[M+H]^+$; found 345.2068.

Intramolecular [2 + 2] photocycloaddition of (±)-17—Formation of cycloadduct (±)-18: A yellow solution of (±)-**17** (8 mg, 23 μmol) in benzene (3 mL) was irradiated with a sunlamp for 15 min at room temperature. During the course of the reaction the yellow color of the starting solution faded. After evaporation of the solvent and purification of the resulting residue by flash column chromatography (silica gel, EtOAc/hexane 1:6), the [2 + 2]-cycloadduct (±)-**18** (7.3 mg, 91 %) was obtained as a colorless glass. $R_f = 0.39$ (silica gel, EtOAc/hexane 1:2); IR (film): $\tilde{\nu}_{max} = 3448$ (w) (OH), 2924 (s), 1728 (w), 1662 (s) (C=O), 1456 (m), 1373 (w), 1296 (m), 1263 (m), 1119 (m), 1019 (m), 803 cm^{-1} (m); ^1H NMR (600 MHz, $CDCl_3$): $\delta = 4.84$ (d, $J = 0.9$ Hz, 1H), 4.60 (br s, 1H), 4.21 (m, 1H), 3.91 (s, 3H), 3.50 (dd, $J_1 = 9.9$ Hz, $J_2 = 6.6$ Hz, 1H), 3.47 (d, $J = 9.9$ Hz, 1H), 2.84 (m, 1H), 2.81 (m, 1H), 2.56 (m, 1H), 2.27 (ddd, $J_1 = 15.8$ Hz, $J_2 = 10.9$ Hz, $J_3 = 4.9$ Hz, 1H), 2.00 (ddd, $J_1 = 13.5$ Hz, $J_2 = 9.3$ Hz, $J_3 = 6.9$ Hz, 1H), 1.94 (s, 3H), 1.84 (s, 3H), 1.47 (d, $J = 7.5$ Hz, 3H), 1.46 (m, 1H), 1.39 (m, 1H), 0.78 (d, $J = 7.5$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 199.6$, 195.7, 160.1, 144.6, 133.3, 110.5, 66.2, 60.3, 58.0, 54.7, 49.6, 49.1, 43.7, 38.6, 38.2, 36.3, 34.7, 23.5, 19.7, 17.7, 10.3; HRMS (MALDI): calcd for $C_{21}H_{29}O_4$: 345.2060 $[M+H]^+$; found 345.2059.

Intramolecular [4+2] cycloaddition of (±)-17—Formation of Diels–Alder adduct (±)-19: A yellow solution of (±)-**17** (5.6 mg, 16 μmol) in dry toluene (2 mL) was heated in a sealed tube at 180 °C (oil bath temperature) for 5 h in the dark. The reaction mixture was allowed to cool down to room temperature, the solvent was removed in vacuo, and the resulting residue was purified by flash column chromatography (silica gel, EtOAc/hexane 1:6) to obtain (±)-**19** (5.0 mg, 89 %) as a colorless glass. $R_f = 0.38$ (silica gel, EtOAc/hexane 1:2); IR (film): $\tilde{\nu}_{max} = 3507$ (br m) (OH), 2931 (s), 1666 (s) (C=O), 1625 (m), 1443 (m), 1378 (w), 1296 (w), 1126 cm^{-1} (m); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 5.72$ (br s, 1H), 4.15 (br s, 1H), 3.87 (s, 3H), 3.53 (br m, 1H), 2.49 (m, 1H), 2.42 (br d, $J = 18.6$ Hz, 1H), 2.21 (m, 2H), 2.01 (br d, $J = 18.6$ Hz, 1H), 1.90 (m, 1H), 1.83 (s, 3H), 1.76 (m, 1H), 1.68 (m, 1H), 1.55 (br s, 3H), 1.54 (m, 1H), 1.36 (d, $J = 7.0$ Hz, 3H), 1.30 (br s, 1H), 1.18 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 201.8$, 198.8, 156.5, 130.1, 128.7, 127.2, 66.5 (2C), 59.7, 52.0, 48.0, 39.8, 39.1, 36.9, 35.0, 34.1, 28.4, 22.8, 17.1, 15.5, 10.1; HRMS (MALDI): calcd for $C_{21}H_{29}O_4$: 345.2060 $[M+H]^+$; found 345.2059. NOE experiments: irradiation of the signal at $\delta = 4.15$ (H_5) effects the signals at $\delta = 1.90$ (1.8 %, H_6) and 1.18 (0.75 %, Me_{19}); irradiation of the signal at $\delta = 1.36$ (Me_{18}) effects the signal at $\delta = 2.42$ (0.8 %, $H_{12\beta}$).

Cyclic sulfone 28 from homochiral diene 27: A sealable tube was charged with homochiral diene **27** (295 mg, 0.60 mmol) and cooled to −78 °C. Then, SO_2 (ca. 4 mL) was condensed into the tube which was then sealed. The reaction mixture was allowed to reach room temperature and stirred for 30 min. Thereafter, the tube was cooled to −20 °C before it was opened to allow evaporation of the SO_2. The resulting residue was purified by flash column chromatography (silica gel, EtOAc/hexane 1:5) to afford chiral sulfone **28** (301 mg, 91 %) as a colorless oil. The compound is a mixture of two diastereoisomers at C_9 (ratio 1.3:1). $R_f = 0.31$ (silica gel, EtOAc/hexane 1:4); IR (film): $\tilde{\nu}_{max} = 2929$ (s), 1461 (m), 1408 (m), 1307 (m), 1249 (w), 1110 (m), 1067 (m), 1014 (w), 838 (m), 779 cm^{-1} (w); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 5.41$ (m, 1H, major), 5.30 (m, 1H, minor), 4.23 (m, 1H, major, 1H, minor), 3.81 (s, 3H, major), 3.80 (s, 3H, major), 3.79 (s, 3H, minor), 3.78 (s, 3H, minor), 3.68 (s, 3H, major), 3.67 (s, 3H, minor), 3.54 (m, 2H, major, 1H, minor), 3.45 (m, 1H, major, 1H, minor), 3.29 (br m, 1H, minor), 3.23 (m, 1H, major, 1H, minor), 3.01 (m, 1H, major, 1H, minor), 2.26 (br m, 1H, major), 2.19 (s, 3H, major, 3H, minor), 2.18 (m, 2H, minor), 2.05 (m, 1H, major), 1.75 (s, 3H, major, 3H, minor), 1.55–1.41 (m, 2H, major, 2H, minor), 1.26 (d, $J = 7.0$ Hz, 6H, major), 1.24 (d, $J = 7.0$ Hz, 3H, minor), 1.20 (d, $J = 7.0$ Hz, 3H, minor), 1.15 (m, 1H, minor), 1.00 (m, 1H, major), 0.94 (2 s, 9H, major, 9H, minor), 0.12 (s, 6H, major), 0.11 (2s, 6H, minor); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 152.8$ (minor), 152.6 (major), 150.3 (minor), 150.2 (major), 147.6 (major), 147.5 (minor), 133.5 (major), 133.2 (minor), 131.7 (minor), 131.6 (major), 126.9 (major), 126.8 (minor), 125.1 (major), 124.0 (minor), 123.2 (minor), 122.9 (major), 68.2 (major), 68.1 (minor), 65.1 (minor), 64.6 (major), 60.4 (2C, major, minor), 60.0 (2C, major, minor), 59.6 (2C, major, minor), 59.0 (major), 58.7 (minor), 45.6 (major), 45.5 (minor), 34.9 (minor), 34.7 (major), 33.9 (major), 33.7 (minor), 30.6 (minor), 30.4 (major), 29.3 (2C, major, minor), 26.0 (major, minor), 23.8 (minor), 23.6 (major), 23.0 (minor), 22.9 (major), 18.8 (2C, minor, major), 18.3 (2C, major, minor), 9.6 (2C, major, minor), −4.5 (2C, major, minor), −4.7 (2C, major, minor); HRMS (MALDI): calcd for $C_{29}H_{48}O_6SSiNa$: 575.2833 $[M+Na]^+$; found 575.2834.

Oxidative demethylation of chiral aromatic sulfone 28 to chiral sulfone-quinone 29: Aqueous HNO_3 (6 M, 1 mL, 6.0 mmol, 12 equiv) was added at room temperature to a solution of the chiral aromatic sulfone **28** (275 mg, 0.50 mmol) in 1,4-dioxane (9 mL) and the mixture was stirred for 2 h. The flask was wrapped with aluminium foil (exclusion of light), before AgO (371 mg, 3.0 mmol, 6.0 equiv) was added portionwise. After stirring for 1 h, the red reaction mixture was diluted with Et_2O (30 mL) and washed with water (3 × 10 mL). The organic phase was dried ($MgSO_4$) and concentrated, and the resulting red residue was purified by flash column chromatography (silica gel, EtOAc/hexane 1:2 → 1:1) to afford two diastereomers of chiral sulfone-quinone **29** (161 mg, 79 %). More polar diastereomer: yellow syrup. $R_f = 0.23$ (silica gel, EtOAc/hexane 1:1); $[\alpha]_D^{25} = -1.2$ ($c = 1.1$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 3512$ (w) (OH), 2936 (m), 1723 (w), 1649 (m) (C=O), 1608 (m), 1448 (m), 1301 (s), 1222 (m), 1111 (m), 911 (m), 732 cm^{-1} (m); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 5.71$ (m, 1H), 4.13 (m, 1H), 3.98 (s, 3H), 3.69–3.56 (m, 3H), 3.12 (m, 2H), 2.09 (m, 1H), 1.94

(s, 3H), 1.85 (s, 3H), 1.75 (m, 2H), 1.60 (m, 1H), 1.47 (m, 1H), 1.17 (d, J = 7.0 Hz, 3H), 1.16 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 188.3, 182.8, 155.7, 144.8, 142.1, 132.8, 128.8, 123.2, 66.7, 64.8, 60.9, 58.7, 42.7, 34.3, 30.8, 28.3, 21.9, 20.4, 19.0, 14.2, 9.0; HRMS (MALDI): calcd for $C_{21}H_{28}O_6S$: 408.1601 $[M]^+$; found 408.1600. Less polar diastereomer: yellow syrup. R_f = 0.34 (silica gel, EtOAc/hexane 1:1); $[\alpha]_D^{25}$ = +99.8 (c = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.51 (m, 1H), 4.10 (m, 1H), 3.99 (s, 3H), 3.59 (m, 2H), 3.49 (m, 1H), 3.15 (m, 2H), 2.17 (m, 1H), 1.92 (s, 3H), 1.81 (brs, 3H), 1.74 (m, 2H), 1.60 (m, 1H), 1.50 (m, 1H), 1.21 (d, J = 7.0 Hz, 3H), 1.15 (d, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 188.6, 182.9, 155.7, 145.4, 142.2, 132.0, 128.3, 124.7, 66.8, 64.9, 60.8, 59.4, 41.4, 35.0, 33.8, 31.7, 28.4, 21.9, 20.8, 18.8, 9.5.

Formation of the skeleton of colombiasin A starting from chiral sulfone-quinone 29—Diels–Alder adduct (−)-30: A yellow solution of chiral sulfone-quinone **29** (mixture of the two diastereomers, 120 mg, 0.29 mmol) in dry toluene (20 mL) was heated in a sealed tube protected from light (aluminum foil) at 180 °C (oil bath temperature) for 20 min. As the reaction progressed, the yellow solution became lighter. The reaction mixture was allowed to cool down to room temperature, the solvent was removed in vacuo and the resulting residue was purified by flash column chromatography (silica gel, EtOAc/hexane 1:6) to furnish exclusively (−)-**30** (89 mg, 89%) as a colorless glass. R_f = 0.37 (silica gel, EtOAc/hexane 1:2); $[\alpha]_D^{25}$ = −164.4 (c = 3.2, $CDCl_3$); IR (film): $\tilde{\nu}_{max}$ = 3488 (brw) (OH), 2930 (m), 1672 (s) (C=O), 1628 (m), 1446 (m), 1294 (m), 1115 cm^{-1} (m); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.67 (brs, 1H), 3.98 (brm, 1H), 3.87 (s, 3H), 3.10 (brm, 1H), 2.38 (brd, J = 18.4 Hz, 1H), 2.34 (m, 2H), 2.06 (m, 1H), 1.95 (brd, J = 18.4 Hz, 1H), 1.93 (dd, J_1 = 5.5 Hz, J_2 = 2.6 Hz, 1H), 1.86 (s, 3H), 1.83–1.74 (m, 2H), 1.65 (brs, 1H), 1.62 (m, 1H), 1.55 (brs, 3H), 1.33 (d, J = 7.3 Hz, 3H), 0.91 (d, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 202.3, 198.5, 155.7, 131.5, 129.4, 124.9, 67.2, 63.7, 59.7, 52.7, 51.4, 41.3, 38.2, 37.0, 34.7, 33.4, 28.7, 22.7, 22.4, 17.7, 10.3; HRMS (MALDI): calcd for $C_{21}H_{29}O_4$: 345.2060 $[M+H]^+$; found: 345.2058.

Formation of the xanthate ester of alcohol (−)-30: Under an argon atmosphere, (−)-**30** (32 mg, 93 μmol) was dissolved in dry THF (1.5 mL) and NaH (60% suspension in mineral oil, 19 mg, 0.47 mmol, 5.0 equiv) was added at room temperature. The reaction mixture was stirred for 30 min before CS_2 (0.47 g, 6.2 mmol, 67 equiv) was introduced into the flask and stirring was continued for another 30 min. Then, MeI (0.85 g, 6.0 mmol, 65 equiv) was added and the reaction mixture was heated to 50 °C for 2 h. After cooling to ambient temperature, the reaction mixture was filtered and concentrated and the resulting residue was purified by flash column chromatography (silica gel, EtOAc/hexane 1:20) to afford the (−)-xanthate ester (38 mg, 95%) as a colorless syrup. R_f = 0.60 (silica gel, EtOAc/hexane 1:2); $[\alpha]_D^{25}$ = −90.3 (c = 3.6, $CDCl_3$); IR (film): $\tilde{\nu}_{max}$ = 2931 (m), 1675 (s) (C=O), 1626 (m), 1451 (m), 1368 (w), 1294 (m), 1208 (s), 1136 (m), 1054 cm^{-1} (s); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.98 (m, 1H), 5.72 (brs, 1H), 3.90 (s, 3H), 3.09 (brm, 1H), 2.56 (s, 3H), 2.43 (brd, J = 18.3 Hz, 1H), 2.22 (m, 2H), 2.11 (m, 2H), 2.01 (m, 2H), 1.88 (s, 3H), 1.83 (m, 1H), 1.66 (ddd, J_1 = 15.0 Hz, J_2 = 11.7 Hz, J_3 = 3.3 Hz, 1H), 1.58 (brs, 3H), 1.34 (d, J = 7.4 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 215.6, 201.6, 197.8, 155.9, 131.3, 129.6, 124.6, 80.1, 63.5, 59.8, 51.2 (2C), 41.1, 36.9, 34.6, 34.1, 34.0, 29.6, 22.7, 22.2, 18.9, 17.4, 10.3.

The same procedure was applied to convert the 7-*epi*-[4+2]-alcohol (±)-**19** into the respective (±)-7-*epi*-[4+2]-xanthate ester: colorless syrup. R_f = 0.58 (silica gel, EtOAc/hexane 1:2); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.85 (m, 1H), 5.78 (brs, 1H), 3.89 (s, 3H), 3.41 (m, 1H), 2.59 (s, 3H), 2.43 (brd, J = 18.2 Hz, 1H), 2.31–2.20 (m, 3H), 2.19–2.05 (m, 3H), 1.85 (s, 3H), 1.73 (m, 1H), 1.59 (m, 1H), 1.58 (brs, 3H), 1.34 (d, J = 7.0 Hz, 3H), 0.91 (d, J = 7.0 Hz, 3H).

Radical deoxygenation—*O*-Methyl colombiasin A [(−)-31]: AIBN (0.2 mg, 1.4 μmol, 0.1 equiv) and nBu$_3$SnH (20 mg, 70 μmol, 5.0 equiv) were sequentially added under an argon atmosphere at room temperature to a solution of the homochiral xanthate ester derived from alcohol (−)-**30** (6.0 mg, 14 μmol) in dry toluene (1 mL). The mixture was carefully deoxygenated by bubbling argon through it for 30 min. The reaction flask was then immersed into a preheated oil bath (110 °C) and the mixture was stirred at this temperature for 30 min. After cooling to ambient temperature, the solvent was evaporated and the resulting residue was purified by flash column chromatography (silica gel, hexane → EtOAc/hexane 1:20). The nonpolar tin compounds were removed by pure hexane as an eluent, whereas product (−)-**31** was eluted by slightly increasing the polarity of the eluent. Thus, (−)-**31** (3.5 mg, 77%) was obtained as a colorless glass. R_f = 0.65 (silica gel, EtOAc/hexane 1:2); $[\alpha]_D^{25}$ = −168.2 (c = 1.1, $CDCl_3$); IR (film): $\tilde{\nu}_{max}$ = 2925 (s), 1728 (w), 1675 (s) (C=O), 1629 (m), 1453 (m), 1268 (m), 1139 (m), 1108 cm^{-1} (m); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.66 (brs, 1H), 3.88 (s, 3H), 3.01 (brm, 1H), 2.41 (brd, J = 19.0 Hz, 1H), 2.12 (m, 1H), 1.91 (brd, J = 19.0 Hz, 1H), 1.89 (s, 3H), 1.89–1.78 (m, 5H), 1.57 (brs, 3H), 1.36–1.29 (m, 3H), 1.32 (d, J = 7.0 Hz, 3H), 0.82 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 203.1, 198.7, 155.1, 131.5, 129.5, 123.5, 63.5, 59.8, 51.6, 48.3, 39.6, 39.0, 36.6, 34.1, 33.6, 31.9, 31.1, 22.8, 22.2, 17.8, 10.4; HRMS (MALDI): calcd for $C_{21}H_{29}O_3$: 329.2111 $[M+H]^+$; found 329.2105.

The same procedure was applied to convert the (±)-7-*epi*-[4+2]-xanthate ester obtained from alcohol (±)-**19** into *O*-methyl 7-*epi*-colombiasin A [(±)-**20**]: colorless glass. R_f = 0.65 (silica gel, EtOAc/hexane 1:2); IR (film): $\tilde{\nu}_{max}$ = 2929 (s), 2355 (m), 1673 (s) (C=O), 1625 (w), 1448 (m), 1373 (w), 1290 (m), 1142 (m), 1114 (m), 1008 cm^{-1} (w); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.66 (brs, 1H), 3.87 (s, 3H), 3.15 (brm, 1H), 2.37 (brd, J = 18.1 Hz, 1H), 2.27 (m, 1H), 2.07 (m, 1H), 1.99 (brd, J = 18.1 Hz, 1H), 2.00–1.90 (m, 2H), 1.85 (s, 3H), 1.67 (m, 1H), 1.59 (m, 1H), 1.55 (brs, 3H), 1.47–1.35 (m, 2H), 1.34 (d, J = 7.0 Hz, 3H), 1.28 (m, 1H), 0.90 (d, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 202.1, 198.7, 156.2, 129.7, 129.2, 125.2, 66.8, 59.7, 51.7, 43.8, 36.7, 36.6, 34.2, 34.1, 33.3, 30.7, 24.3, 22.8, 17.3, 15.7, 9.9; HRMS (MALDI): calcd for $C_{21}H_{29}O_3$: 329.2111 $[M+H]^+$; found 329.2103.

Colombiasin A [(−)-1], Δ^{11,12}-colombiasin A [(−)-1‴], and 7-*epi*-colombiasin A [(±)-1′]: (*Z*)-Cyclooctene (40 mg, 0.36 mmol, 20 equiv) was added under an argon atmosphere to a solution of *O*-methyl colombiasin A [(−)-**31**] (6 mg, 18 μmol) in dry CH_2Cl_2 (1 mL). The reaction mixture was then cooled to −78 °C, before a solution of BBr_3 (1M in CH_2Cl_2, 0.18 mL, 0.18 mmol, 10 equiv) was added dropwise. The reddish reaction mixture was stirred for 30 min (−78 °C) and was then quenched by adding saturated aqueous $NaHCO_3$ solution (1 mL). Longer reaction times led to an increased formation of by-products. The cooling bath was removed and the mixture was stirred at room temperature for another 30 min. The mixture was diluted with CH_2Cl_2 (3 mL) and the organic phase was washed with brine (1 mL), dried over $MgSO_4$, and concentrated. Purification of the resulting residue via preparative TLC (silica gel, EtOAc/hexane 1:8) recovered unreacted (−)-**31** (1.8 mg, 30%) and furnished (−)-colombiasin A (**1**) (1.7 mg, 43% based on 70% conversion) as a colorless powder. R_f = 0.62 (silica gel, EtOAc/hexane 1:2); $[\alpha]_D^{25}$ = −61.0 (c = 0.1, $CHCl_3$); IR (film): $\tilde{\nu}_{max}$ = 3373 (w) (OH), 2925 (s), 2860 (m), 1665 (s) (C=O), 1452 (w), 1383 (m), 1350 (w), 1262 (w), 1089 (s), 1023 (s), 803 cm^{-1} (m); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.90 (s, 1H), 5.68 (brs, 1H), 3.05 (brm, 1H), 2.41 (brd, J = 19.1 Hz, 1H), 2.13 (m, 1H), 1.96–1.88 (m, 3H), 1.90 (s, 3H), 1.87–1.76 (m, 3H), 1.59 (m, 1H), 1.57 (brs, 3H), 1.37 (d, J = 7.0 Hz, 3H), 1.35–1.22 (m, 2H), 0.81 (d, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 202.6, 199.6, 149.5, 128.9, 123.8, 120.3, 64.0, 51.6, 48.2, 39.5, 38.7, 36.3, 33.6, 33.5, 31.8, 31.1, 22.8, 22.1, 17.7, 9.7; HRMS (MALDI): calcd for $C_{20}H_{27}O_3$: 315.1955 $[M+H]^+$; found 315.1961.

When the same procedure was used, however without (*Z*)-cyclooctene, colombiasin A [(−)-**1**] was formed in 30% yield, along with Δ^{11,12}-colombiasin A [(−)-**1‴**] (1.1 mg, 20%). (−)-**1‴**: colorless powder. R_f = 0.63 (silica gel, EtOAc/hexane 1:2); $[\alpha]_D^{25}$ = −62.8 (c = 0.1, $CHCl_3$); IR (film): $\tilde{\nu}_{max}$ = 3378 (w) (OH), 2926 (s), 2849 (m), 1661 (s) (C=O), 1455 (m), 1380 (m), 1356 (m), 1259 (w), 1155 (m), 1099 cm^{-1} (m); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.96 (s, 1H), 5.34 (brs, 1H), 2.61–2.49 (m, 2H), 2.13 (m, 1H), 2.03 (m, 1H), 1.92–1.81 (m, 4H), 1.89 (s, 3H), 1.66 (s, 3H), 1.56 (m, 1H), 1.44 (m, 1H), 1.33 (d, J = 7.0 Hz, 3H), 1.32–1.24 (m, 2H), 0.88 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 202.9, 198.9, 150.5, 139.9, 123.5, 121.4, 60.4, 54.8, 48.9, 40.4, 40.1, 37.7, 35.8, 33.4, 32.1, 30.8, 23.8, 22.3, 17.8, 9.8; ESIMS (negative) ($C_{20}H_{26}O_3$): m/z (%): 313 (50) $[M-H]^+$.

The same procedure, however without (*Z*)-cyclooctene, was applied to convert *O*-methyl 7-*epi*-colombiasin A [(±)-**20**] into 7-*epi*-colombiasin A [(±)-**1′**]: colorless powder. R_f = 0.62 (silica gel, EtOAc/hexane 1:2); IR (film): $\tilde{\nu}_{max}$ = 3373 (w) (OH), 2927 (s), 2861 (m), 1659 (s) (C=O), 1451 (m), 1381 (m), 1349 (m), 1099 cm^{-1} (m); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.95 (s, 1H), 5.68 (brs, 1H), 3.16 (brm, 1H), 2.41 (brd, J = 17.6 Hz, 1H), 2.31 (m, 1H), 2.11–1.92 (m, 4H), 1.88 (s, 3H), 1.71 (m, 1H), 1.60 (m, 1H), 1.55 (brs, 3H), 1.40 (m, 1H), 1.39 (d, J = 7.0 Hz, 3H), 1.35–1.23 (m, 2H), 0.89 (d, J = 6.3 Hz, 3H); HRMS (MALDI): calcd for $C_{20}H_{27}O_3$: 315.1955 $[M+H]^+$; found 315.1964.

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