217. Enantioselective Syntheses and Absolute Configurations of Viridiene and Aucantene, Two Constituents of Algae Pheromone Bouquets

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Dedicated to Prof. Dr. *F. Lingens* on the occasion of his 60th birthday

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Viridiene ((+)-**6**; (+)-(3*R*,4*S*)-3-((1*Z*)-1,3-butadienyl)-4-vinylcyclopentene) and aucantene ((+)-**18**; (+)-(4*R*,5*R*)-4-((1*E*)-1-propenyl)-5-vinylcyclohexene) are constituents of the pheromone bouquets of several brown algae species. Key synthons to the title compounds are optically active γ-lactones with known or experimentally determined absolute configurations. Horse liver alcohol dehydrogenase, which catalyses the oxidation of *meso*- and racemic non-*meso* diols to chiral lactones, and pig-liver esterase, which catalyzes the saponification of *meso*-diesters to chiral half-esters, were utilized for the asymmetric synthesis of such precursors. The racemic non-*meso* diol *rac*-**1** is converted to the two stereoisomeric γ-lactones (+)-**2** and (+)-**3** which are readily separated. *meso*-Diol **12** is oxidized to the chiral γ-lactone (−)-**11**. Its enantiomer (+)-**11** is obtained by enantioselective saponification of the *meso*-diester **9** with pig-liver esterase. Appropriately designed syntheses lead from these chiral intermediates to both enantiomers (+)- and (−)-**6** of viridiene and (+)- and (−)-**18** of aucantene. In addition, kinetically controlled reduction of the racemic aldehydes *rac*-**5a** and *rac*-**15** with horse liver alcohol dehydrogenase offers a convenient alternative to the enantioselective preparation of the enantiomers of the two hydrocarbons **6** and **18**. Chromatography of **6** on triacetylated cellulose as a stationary chiral phase confirms the enantiospecificity of the synthetic routes designed.

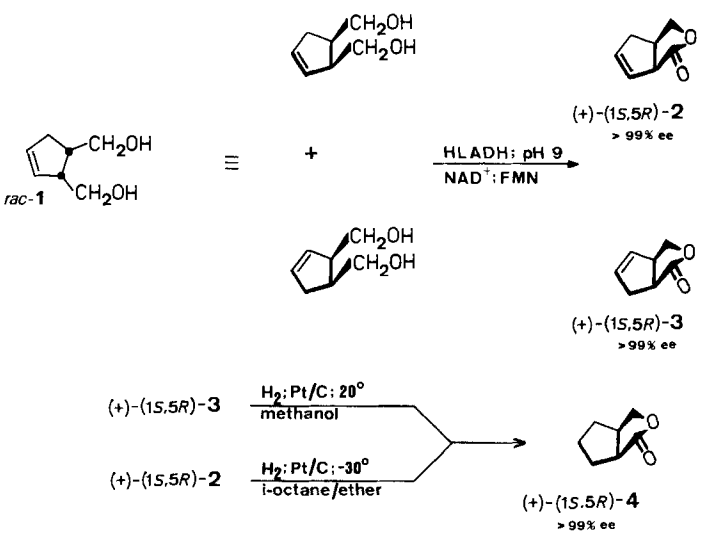
1. Introduction. – The inter- and intraspecific communication between sexual gametes of brown algae *(Phaeophyceae)* is mediated by chemical-signal compounds given off by the female cell. The bio-active messengers must interact with exactly shaped recognition sites on the conspecific males [1]. The configurational and chiral characterization of the messenger compounds is necessary for a complete description of these enantioselective biological signal systems. This, however, is difficult in most cases due to the extremely small amounts of the pheromones isolated from natural sources. Mostly, only very diluted samples are available (*ca.* 0.1–1 µg/ml) which do not allow the application of chiroptical methods. Also complexation gaschromatography [2] failed with algal pheromones because of competing side reactions. We therefore followed the inverse strategy by synthesizing enantiomerically pure compounds and assaying their activity on androgametes of brown algae. A first application of this concept with synthetic (+)- and (−)-multifidene, *cis*-3-((1*Z*)-1-butenyl)-4-vinylcyclopentene, (> 98% ee each) and androgametes of *Cutleria multifida* established that both enantiomers in this interaction system are distinguished by at least two orders of magnitude [3].

These results, and the extant lack of sufficiently discriminative and sensitive analytical methods encouraged us to proceed with this approach. We report here the first enantiospecific/selective synthesis of both enantiomers of viridiene (**6**), the pheromone for *Syringoderma phinneyi* [4] and *Desmarestia* species [5], as well as of aucantene (**18**), which had been isolated as a biologically inactive by-product of the pheromone bouquet of *Cutleria multifida* [6].

Application of the well documented high enantioselectivity of horse liver alcohol dehydrogenase (HLADH) or pig-liver esterase (PLE) [7] [8] towards *meso*-compounds or other substrates with prochiral centers avoids the formation and subsequent need for chromatographic resolution of diastereoisomeric intermediates and makes γ-lactones of defined configuration easily accessible as synthetic intermediates. The absolute configuration of the final pheromone products can be directly determined by correlating the biological activity of the most active enantiomer to the absolute configuration of its corresponding γ-lactone precursor.

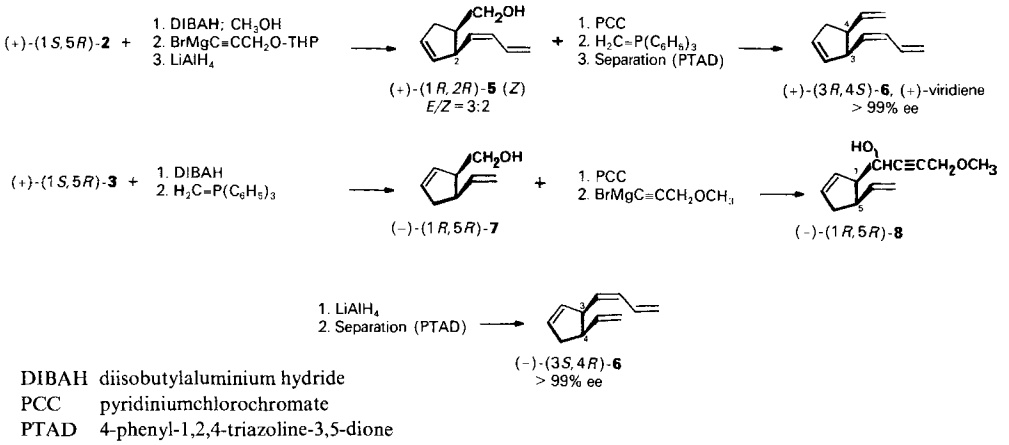
2. Enantiospecific Synthesis of (+)- and (−)-Viridiene ((+)- and (−)-6, resp.). – For the synthesis of both enantiomers of viridiene (**6**), we closely followed our published synthetic approach to the racemic pheromone [9], but used horse liver alcohol dehydrogenase (HLADH) for enantiospecific oxidation of the diol *rac*-**1** to the appropriately functionalized chiral key-synthons. The enzyme is able to discriminate between constitutionally identical enantiotopic groups attached to centers of opposite chirality in *meso*-compounds [7], hence the non-*meso*-diol *rac*-**1** is transformed into the two isomeric, but enantiomerically pure γ-lactones (+)-**2** and (+)-**3** *(Scheme 1)*, which serve as starting materials for the synthesis of both enantiomers of viridiene, namely (+)-**6** from (+)-**2** and (−)-**6** from (+)-**3** *(Scheme 2)*.

Scheme 1



HLADH horse liver alcohol dehydrogenase
NAD^+ nicotinamide adenine dinucleotide
FMN *flavin mononucleotide*

Scheme 2



DIBAH diisobutylaluminium hydride
PCC pyridiniumchlorochromate
PTAD 4-phenyl-1,2,4-triazoline-3,5-dione

Oxidation of *rac*-**1** with NAD^+ in the presence of HLADH immobilized on CNBr-activated *Sepharose* [10] and flavine mononucleotide (FMN) yielded the expected γ-lactones (+)-**2** and (+)-**3** in essentially pure form. Both compounds were readily separated by MPLC on silica gel with isooctane/Et_2O. Their absolute configuration and optical purity was established by catalytic hydrogenation to the known saturated γ-lactone (+)-**4**, which was obtained in > 99% chemical and optical purity from both compounds [11] *(Scheme 1)*.

Treatment of lactone (+)-**2** first with equiv. amounts of diisobutylaluminium hydride (DIBAH) and CH_3OH in toluene at −78°, then with excess (3-(tetrahydro-2-pyranyloxy)-1-propynyl)magnesium bromide yielded an acetylenic intermediate which was reduced with $LiAlH_4$ to the butadienyl-alcohol (+)-**5** as a (*E*)/(*Z*)-mixture (ratio 3:2; *Scheme 2*). Oxidation of (+)-**5** with pyridinium chlorochromate (PCC) gave an unstable aldehyde; its subsequent *Wittig* olefination with methylidene(triphenyl)phosphorane led to the natural enantiomer of viridiene, (+)-**6**, which was obtained isomerically pure after removal of the (*E*)-isomer by *Diels-Alder* reaction with the selective dienophile 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) [9].

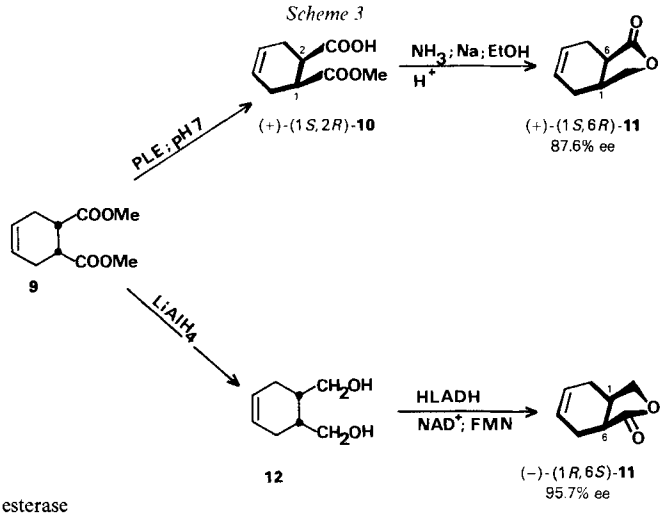
The (−)-enantiomer of **6** was obtained by a similar sequence of reactions *(Scheme 2)*: Lactone (+)-**3** was converted by treatment with DIBAH and methylidene-(triphenyl)phosphorane to the alcohol (−)-**7** [12]. Oxidation of (−)-**7** with PCC gave the unstable β,γ-unsaturated aldehyde which was immediately alkylated with 3 equiv. of (3-methoxy-1-propynyl)magnesium bromide to yield the acetylenic intermediate (−)-**8**. Reduction of (−)-**8** with excess $LiAlH_4$ [13] removed all O-substituents and led predominantly to the (*Z*)-olefine (−)-**6**. The (*Z*)/(*E*)-isomer ratio was 4:1 (GC), and the pure (*Z*)-alkene (−)-**6** was obtained as described for (+)-**6**.

The biological activity of the two viridiene enantiomers on *Syringoderma* androgametes was determined by the droplet assay [14] [15]; it showed a tenfold preference for (+)-**6** [16]. In conclusion, the absolute configuration of (+)-viridiene is 3*R*,4*S* related to the absolute configuration of the starting lactone (+)-**2**. This result was also confirmed by chromatographic comparison on triacetylated cellulose of the *Syringoderma* pheromone and the synthetic viridiene enantiomers [17] *(vide infra)*.

3. Enantioselective Synthesis of (+)- and (−)-Aucantene ((+)- and (−)-18, resp.). – (+)-Aucantene ((+)-**18**) was first isolated from the Mediterranean brown alga *Cutleria multifida* [6]; its structure and geometry were deduced from MS and ^{1}H-NMR data and confirmed by synthesis [18]. The small amount of natural material, however, made it impossible to work out the absolute configuration of this particular enantiomer by specific degradations. Enantioselective synthesis of both aucantene enantiomers and subsequent determination of their sign of rotation promised more success.

Since already our original synthesis of (±)-aucantene [18] started with a racemic γ-lactone, a modified sequence based on the preparation of chiral γ-lactone precursors was the method of choice. Oxidation of the diol **12** with immobilized HLADH gave (−)-**11** in 54% yield and 96% ee with respect to [7] [19] *(Scheme 3)*; this was independently confirmed by ^{1}H-NMR after treatment of (−)-**11** with 3.0 equiv. of MeMgBr and addition of Eu(tfc)$_3$ in analogy to [20]. The (+)-enantiomer of the lactone **11** was obtained by enantioselective saponification of the *meso*-diester **9** to the chiral half-ester intermediate (+)-**10** with pig-liver esterase at pH 7 [8] [26] *(Scheme 3)*. Reduction of the ester

Scheme 3

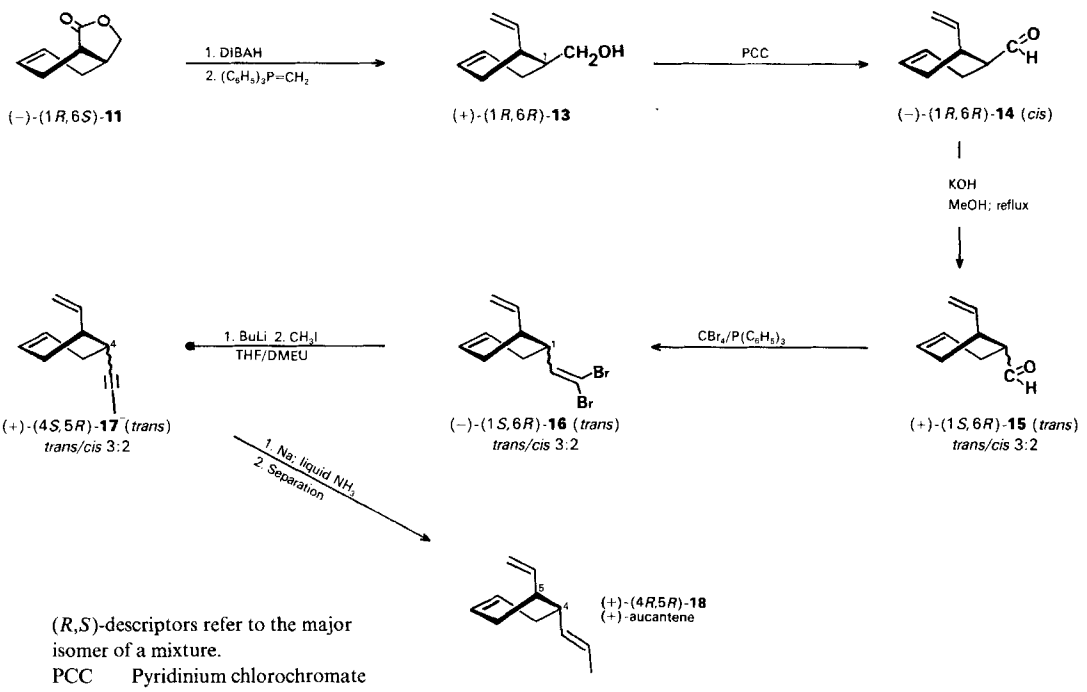


PLE pig-liver esterase
HLADH horse liver alcohol dehydrogenase
NAD^+ nicotinamide adenine dinucleotide
FMN flavin mononucleotide

moiety of (+)-**10** with Na and EtOH in liquid NH_3 [19] [27] followed by brief acidification with dil. HCl gave (+)-**11** in 87% ee with respect to [19]; the original *cis*-configuration remained intact as proven by GC and ^{1}H-NMR. Thus, the two enzymatic methods complement each other giving access to either of the two enantiomeric lactones **11** as already stated by *Gais* and *Lukas* [19].

Reductive olefination of (−)-**11** with DIBAH and methylidene(triphenyl)-phosphorane [12] gave the alcohol (+)-**13** *(Scheme 4)*; its oxidation (PCC) yielded the aldehyde (−)-**14**, which was epimerized to an equilibrium mixture of the *trans*- and *cis*-isomers (+)-**15**/(−)-**14** (ratio 3:2) by treatment with a catalytic amount of KOH in boiling CH_3OH. *Wittig* olefination of this mixture with (dibromomethylidene)-

Scheme 4



(*R*,*S*)-descriptors refer to the major isomer of a mixture.
PCC Pyridinium chlorochromate
DMEU 1,3-dimethyl-2-imidazolidinone
THF Tetrahydrofurane

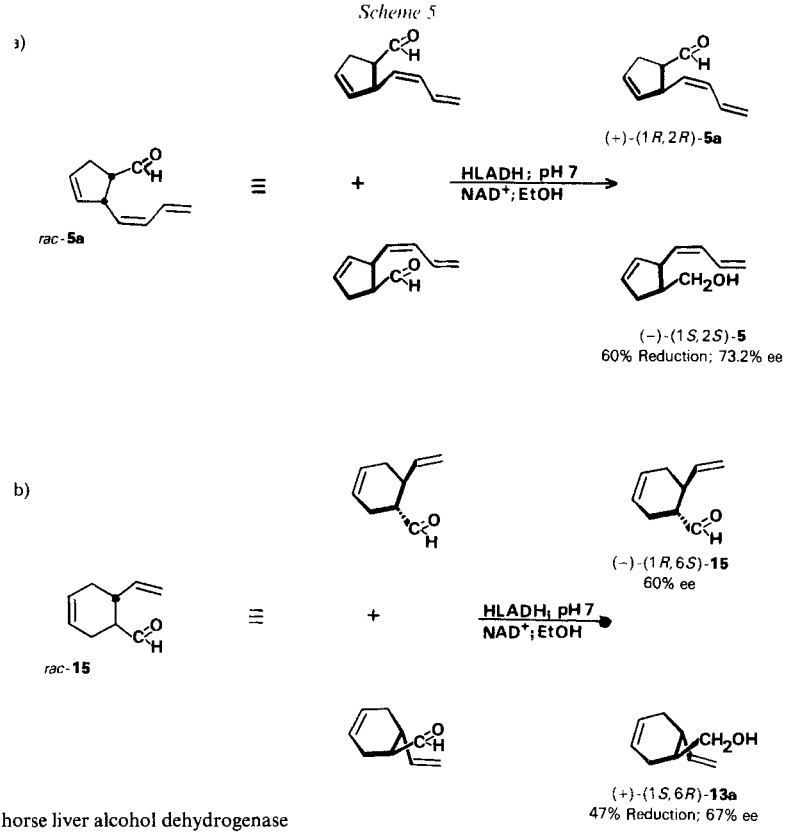
phosphorane at 0° [21] led to the dibromide (−)-**16** and its *cis*-isomer (ratio 3:2). On addition of 2.2 equiv. of BuLi [22] in dry THF/1,3-dimethyl-2-imidazolidinone (DMEU) 9:1, the dibromide mixture was dehydrohalogenated to terminal lithium acetylides. Subsequent alkylation with CH_3I produced the propinyl-derivative (+)-**17** and its *cis*-isomer (ratio 3:2), and stereospecific reduction with Na in liquid NH_3 finally gave a 3:2 mixture of *trans*/*cis*-isomers which was readily separated by chromatography on silver-impregnated silica gel to yield the natural aucantene enantiomer (+)-**18**.

The synthesis of (−)-aucantene followed the same route but starting from (+)-**11**. Details and specific rotations are given in the *Exper. Part*.

Comparing the sign of rotation of the two synthetic enantiomers with naturally secreted (+)-aucantene proves its absolute configuration to be 4*R*,5*R* with respect to the starting lactone (−)-**11**, which was previously shown by X-ray analysis to be 1*R*,6*S* [19].

4. Enantioselective Synthesis of Pheromones by Kinetic Resolution of Racemic-Aldehyde Intermediates. – Another convenient route to unnatural (−)-viridiene ((−)-**6**) was found when the racemic aldehyde *rac*-**5a** [9] was enzymatically reduced at pH 7 (HLADH, NAD^+, EtOH) under kinetically controlled conditions [23]. When the reduction of *rac*-**5a** was allowed to proceed to *ca.* 60% conversion, (−)-**5** was obtained (after chromatography on silica gel) in 44% yield and 73% optical purity relative to (+)-**5**; the unreacted, unstable aldehyde (+)-**5a** could not be isolated by chromatography *(Scheme 5a)*.

Scheme 5



HLADH horse liver alcohol dehydrogenase
NAD^+ nicotinamide adenine dinucleotide

When the reduction of the *trans*-disubstituted cyclohexene carbaldehyde *rac*-**15** [18] was allowed to proceed to 47% conversion, the aldehyde (−)-**15** (60% ee) and alcohol (+)-**13a** (67% ee) were isolated *(Scheme 5b)*. This high ee is remarkable, since the oxidation of a number of racemic *trans*-diols with HLADH yields only lactones of low optical purity (1–16% ee) [7]. The stereochemical outcome in both cases corresponds to the side-specificity of HLADH as deduced from the 'cubic-site model' of the enzyme's active center [24]. Hence, on reduction of the aldehydes *rac*-**5a** and *rac*-**15**, the same spatial conformation of the substrates is involved as on oxidation of the diols *rac*-**1** and **12** (*cf. Scheme 1* and *3*). By following the 'cubic-site analysis' [24], this allows prediction of the absolute configuration of the products obtained.

In this way, unnatural viridiene (−)-**6** and both aucantene enantiomers (+)- and (−)-**18** were prepared from *rac*-**5a** and *rac*-**15** in good yield and acceptable optical purity as confirmed by chromatography on triacetylated cellulose *(vide infra)*.

The kinetic resolution of racemic aldehydes, corresponding in functionalization and substitution to *rac*-**5a** or *rac*-**15**, opens an elegant approach to natural-product synthesis. A more systematic study on scope and limitations of this method is currently under investigation.

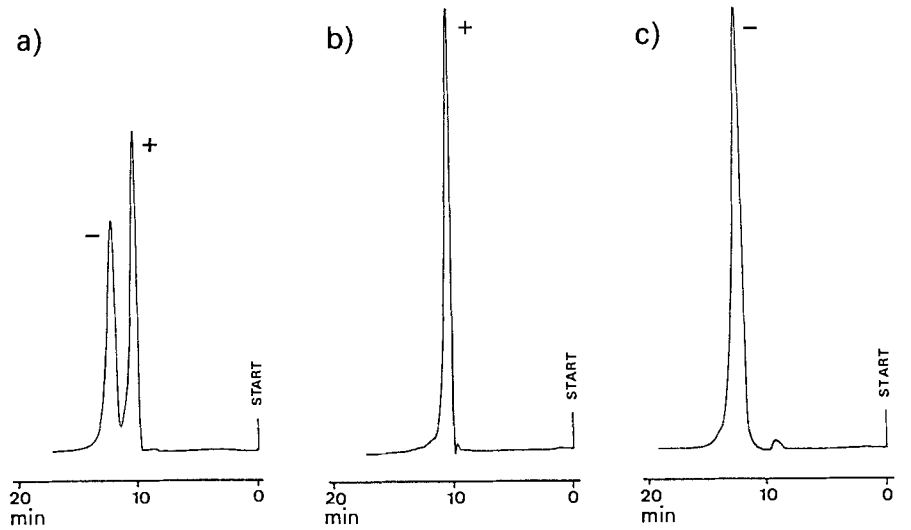


Figure. *Anal. separation of (+)- and (–)-viridiene ((+)- and (–)-***6***, resp.) on triacetylated cellulose* (CEL AC-40 XF; Macherey and Nagel, *Düren, FRG*). Stainless-steel column; 250 × 4 mm. Mobile phase: EtOH/H_2O 9:1. UV-Detection at 230 nm. Sensitivity 2 AU. Flow rate 0.5 ml/min at 23°. (*a*): Injection of 20 µl of a 200 ppm soln. of racemic viridiene in EtOH. (*b*) and (*c*): Chromatography of 20 µl of 200 ppm solns. of synthetic (+)- and (–)-viridiene ((+)-**6** and (–)-**6**), resp., in EtOH. Flow rates and temp. conditions identical with *a*).

5. Analysis of the Enantiomeric Purity of (+)- and (–)-Viridiene ((+)- and (–)-6, resp.). – We recently employed commercial triacetylated cellulose (*CEL AC-40 XF, Macherey and Nagel,* Düren, FRG) as chiral stationary phase for the separation of *genuine* pheromone enantiomers [17]. As shown in *Fig. a,* racemic viridiene (*rac*-**6**) is well separated ($\alpha = 1.6$) by this technique using a slurry-packed column [25] (25 × 0.4 cm) and EtOH/H_2O 4:1 as eluant.

Enantiomer (–)-**6** synthesized according to the method described above gave only a single peak *(Fig. c)*; admixtures of as little as 1.5% of (+)-**6** already formed a distinct signal indicating that the enzymatic conversion of the diol *rac*-**1** had occurred with > 98.5% ee. A similar result was obtained for (+)-**6** *(Fig. b)*.

These findings not only corroborate the known high degree of enantioselectivity of HLADH but also confirm retention of optical integrity during all steps of synthesis. Compound (–)-**6** obtained by kinetic resolution of the racemic aldehyde *rac*-**5a** gave results corresponding to an enantiomer composition of 87:13, thus confirming the optical purity calculated from the specific rotation of (–)-**5**.

The two enantiomers of aucantene (+)- and (–)-**18** did not separate under various chromatographic conditions.

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Experimental Part

General. All solvents and reagents were purified prior to use. Reactions, except the enzymatic conversions, were carried out under an inert atmosphere. Anh. $MgSO_4$ was used for all drying operations. Solns. were generally concentrated by flash evaporation under reduced pressure. CC = column chromatography. Horse liver alcohol dehydrogenase (HLADH) (EC 1.1.1.1), pig-liver esterase (PLE) (EC 3.1.1.1), and nicotinamide adenine dinucleotide (NAD^+), free acid, grade II, were obtained from *Boehringer,* Mannheim, FRG. Flavin mononucleotide (FMN), commercial grade, was purchased from *Sigma Chemie,* Munich, FRG. CNBr-activated *Sepharose 4 B* (*Pharmacia,* Uppsala, Sweden) was used for immobilization of HLADH. The specific activity of the immobilized enzyme was ΔE_{340} min^{-1} mg^{-1} = 8.8 under standard assay conditions [10]. Anal. GC: *Carlo-Erba* gaschromatograph, series *4200,* equipped with *Duran*-glass capillaries (50 m × 0.32 mm) coated with *OV 73.* Prep. GC: stainless-steel columns (1.5 m × 5 mm) filled with *Chromosorb P* (60–80 mesh) coated with 15% *Fractonitril III.* Anal. HPLC: *Altex-420* HPLC system combined with a *Kratos SF 770* variable wavelenght UV monitor. Prep. HPLC: *Knauer* differential refractometer. M.p. and b.p. are uncorrected. $[\alpha]^{25}$: *Carl-Zeiss* precision polarimeter 0.005°. *IR* (cm^{-1}): *Pye-Unicam-SP3-200* spectrophotometer. ^{1}H-NMR: *Varian-EM-390* 90-MHz spectrometer; in CCl_4 with TMS as internal standard. MS (*m/z*): *Finnigan-4510* GC/MS system.

cis-3-Cyclopentene-1,2-dimethanol (*rac*-**1**). A soln. of lactone *rac*-**3** [9] (10.0 g, 81 mmol) in dry THF (30 ml) was slowly added at r.t. to a well stirred suspension of $LiAlH_4$ (2.3 g, 60.4 mmol) in THF (100 ml). Stirring was continued for 30 min at reflux, and excess $LiAlH_4$ was destroyed by slow addition of 5N NaOH (50 ml) after chilling. The granular precipitate was filtered off, washed with EtOAc (2 × 50 ml), and the aq. phase was extracted with EtOAc (2 × 100 ml). After drying and evaporation of the solvent, the crude *rac*-**1** was distilled (b.p. 84–85°/0.003 Torr) to yield 7.4 g (72%) of a colourless, highly viscous oil. IR (neat): 3330, 3060, 2930, 1615, 1445 (br.), 1100, 1060, 1020, 950, 710. ^{1}H-NMR (CCl_4): 1.80–2.78 (*m*, 3 H); 2.95 (br. *m*, 1 H); 3.26–3.73 (*m*, 4 H); 5.00 (*s*, 1 H); 5.40–5.87 (*m*, 2 H). MS (70 eV): 129 (0.04, $M^+ - 1$), 110 (9), 95 (5), 80 (98), 79 (100), 77 (27), 67 (93), 55 (12), 53 (11), 51 (9), 41 (55), 39 (32). Anal. calc. for $C_7H_{12}O$ (128.18): C 65.60, H 9.44; found: C 65.48, H 9.47.

*(+)-(1S,5R)-3-Oxabicyclo[3.3.0]oct-7-en-2-one ((+)-***2***) and (+)-(1S,5R)-3-Oxabicyclo[3.3.0]oct-6-en-2-one (***3***).* Diol *rac*-**1** (2.8 g, 22.2 mmol), NAD^+ (1.2 g, 1.8 mmol), and FMN (16.5 g, 34.5 mmol) were dissolved with stirring in 750 ml of 0.075M glycine/$Na_4P_2O_7$ buffer, pH 9 (1.7 g glycine/33.3 g $Na_4P_2O_7 \cdot 10\ H_2O$ per liter). The pH was readjusted to pH 9 before the *Sepharose*-bound enzyme [10] corresponding to 70 mg HLADH was added. The mixture which was kept suspended by slow stirring turned from its initial orange to a black colour as the reaction proceeded (reaction control by GC *(Apiezon L)*). After 22 h, *rac*-**1** had completely disappeared, and the suspension contained a 1:1 mixture of (+)-**2** and (+)-**3** and *ca.* 5% of hydroxy-aldehyde intermediates. The immobilized enzyme was filtered off (sintered-glass filter *G3*) and washed with 100 ml of 0.05M potassium-phosphate buffer (pH 7). The combined filtrates were acidified to pH 3 with HCl and continuously extracted with $CHCl_3$ for 24 h. After drying and evaporation, a dark brown residue was obtained, which was prepurified by filtration over silica gel to remove FMN and other by-products. Separation of (+)-**2** and (+)-**3** was achieved by low pressure CC on silica gel (column: 2.5 × 30 cm; isooctane/Et_2O 3:2; loaded with 250-mg portions each), monitoring the eluent refractometrically. Lactone (+)-**2** eluted first and was 99.5% isomerically pure (GC) after rechromatography under the same conditions (0.78 g, 57% yield). $[\alpha]^{25}_{578}$ = +352.3° (*c* = 12.71, $CHCl_3$). Lactone (+)-**3** eluted together with *ca.* 15% of (+)-**2** and was further purified by recrystallization from isooctane/Et_2O 2:1 at −30° (0.57 g, 47% yield; 98.8% purity (GC)). $[\alpha]^{25}_{578}$ = +68.9° (*c* = 4.7, $CHCl_3$). Spectroscopic data: see [11].

*Absolute Configuration and Optical Purity of (+)-***2** *and (+)-***3**. Lactone (+)-**3** was hydrogenated over Pt/C in CH_3OH at r.t. to give (+)-**4** with $[\alpha]^{25}_{578}$ = +97.4°, in agreement with an authentic sample [11] [7]. Lactone (+)-**2** was hydrogenated in isooctane/Et_2O 3:2 at −30° (to avoid isomerization of the β,γ-unsaturated double bond [11]) yielding (+)-**4** with $[\alpha]^{25}_{578}$ = +97.5°. Thus, both lactones were obtained with identical absolute configurations and > 99% optical purity.

*(+)-(1R,2R)-2-((1Z)-1,3-Butadienyl)-3-cyclopenten-1-methanol ((+)-***5***).* a) *Reductive Alkylation.* To a cooled soln. (−78°) of (+)-**2** (0.5 g, 4.03 mmol) in dry toluene (10 ml) was slowly added DIBAH (3.5 ml, 6.0 mmol) in dry toluene. Stirring was continued for 45 min, and the aluminate was decomposed by injection of dry CH_3OH (6 mmol). After the gas evolution (*ca.* 10 min), the soln. was rapidly transferred into a second flask containing 3 equiv. of (3-(tetrahydro-2-pyranyloxy)-1-propynyl)magnesium bromide in 100 ml of dry THF (prepared from EtMgBr and the protected propargyl alcohol). After 3 h stirring at 0°, the soln. was poured on ice/NH_4Cl and the aq. phase carefully extrated with Et_2O (3 × 70 ml). The combined extracts were washed with brine, dried, and evaporated to leave 0.9 g of the crude alkylation product.

b) *Removal of O-Substituents.* The alkylation product of *a*) in dry THF (20 ml) was slowly added at 0° to a well stirred suspension of $LiAlH_4$ (0.72 g, 19 mmol). The temp. was raised to 40° and kept for 1 h. After cooling (0°),

$AlCl_3$ (20 mg) was added and the mixture brought to reflux for 1 h. The soln. was chilled again and slowly(!) poured onto ice/dil. HCl. Following extraction with Et_2O (3 × 80 ml), washing with sat. $NaHCO_3$ soln. and brine, drying and evaporation, the crude (+)-**5** was purified by column chromatography on silica gel (hexane/Et_2O 4:1): 0.16 g (27% overall yield from (+)-**2**) of a 85% pure product (GC), which was not further purified. $[\alpha]_{578}^{25} = +214.5$ ($c = 1.212$, CH_2Cl_2). Spectroscopic data: see [9].

*(+)-(3R,4S)-3-((1Z)-1,3-Butadienyl)-4-vinylcyclopentene ((+)-**6**).* A soln. of (+)-**5** (0.15 g, 1.0 mmol) in CH_2Cl_2 (5 ml) was oxidized in the usual manner with PPC (0.86 g, 4.0 mmol). After 2 h, the chromium salts were precipitated with pentane (10 ml) and removed by suction. The soln. was dried and concentrated *i.v.* to about 2 ml. The crude aldehyde was immediately transferred into a soln. of methylidene(triphenyl)phosphorane (4.0 mmol) in 20 ml of dry THF (BuLi as base), followed by 30 min stirring at r.t. Then, pentane (50 ml) was added and the org. phase washed with dil. HCl (2 × 20 ml) and H_2O (20 ml). After drying, the soln. was evaporated to *ca.* 5 ml, and 4-phenyl-1,2,4-triazoline-3,5-dione was added with stirring until the red colour of the reagent just persisted (*ca.* 60 mg). Concentration *i.v.* and CC on silica gel with pure pentane yielded 16.0 mg of configurationally homogeneous (+)-**6** (12.5% overall from (+)-**5**). $[\alpha]_{578}^{25} = +228°$ ($c = 0.224$, pentane). Spectroscopic data: see [9].

*(−)-(1R,5R)-5-Vinyl-2-cyclopenten-1-methanol ((−)-**7**).* At −78°, (+)-**3** (1.0 g, 8.1 mmol) in dry toluene (15 ml) was reduced by slow addition of 1.5M DIBAH (6.4 ml) in dry toluene. Stirring was continued for 45 min, followed by injection of dry CH_3OH (50 µl) to destroy the excess of DIBAH. Subsequently, the cold soln. (−78°) was rapidly transferred into a soln. of methylidene(triphenyl)phosphorane (16 mmol) in dry THF (100 ml). The mixture was stirred for 24 h, and Et_2O (100 ml) was added. After washing with ice/dil. HCl (2 × 50 ml) and brine (50 ml), the org. layer was concentrated to *ca.* 15 ml. Addition of pentane (50 ml) and freezing (−20°, 4 h) precipitated most of the triphenylphosphine oxide, and the clear filtrate was evaporated and purified by CC on silica gel using hexane/Et_2O 4:1. Following removal of solvent, 0.60 g (60%) of pure (−)-**7** were obtained. $[\alpha]_{578}^{25} = -185.4°$ ($c = 1.634$, CH_2Cl_2). Spectroscopic data: see [9].

*(−)-4-Methoxy-1-((1R,5R)-5-vinyl-2-cyclopenten-1-yl)-2-butyn-1-ol ((−)-**8**).* As described for (+)-**6**, (−)-**7** (0.5 g, 4.0 mmol) was oxidized with PCC (4 equiv.). The clear filtrate was concentrated to *ca.* 3 ml and slowly added to a soln. of 10 mmol of (3-methoxy-1-propynyl)magnesium bromide in dry THF (30 ml) at which the mixture turned dark. Stirring was continued at r.t. for 1 h, and then the soln. was poured onto ice/NH_4Cl. The aq. phase was extracted with Et_2O (2 × 50 ml), and the combined org. layers were washed with 2N HCl (20 ml) and H_2O (20 ml). After drying and evaporation, the crude alkynol was chromatographed on silica gel (hexane/Et_2O 4:1). Removal of solvent yielded 0.16 g (31%) of (−)-**8**. $[\alpha]_{578}^{25} = -163.8°$ ($c = 0.629$, CH_2Cl_2). Spectroscopic data: see [9].

*(−)-(3S,4R)-3-((1Z)-1,3-Butadienyl)-4-vinylcyclopentene ((−)-**6**).* To a stirred, chilled suspension of $LiAlH_4$ (0.1 g, 3.1 mmol) in dry THF (10 ml) was slowly added a soln. of (−)-**8** (0.15 g, 0.81 mmol) in dry THF (2 ml). The mixture was stirred at 40° for 1 h followed by cooling (0°) and addition of $AlCl_3$ (10 mg, 0.08 mmol). Then the soln. was refluxed for 1 h, cooled, and slowly poured onto ice/dil. HCl (*ca.* 10%). After extraction with pentane (2 × 20 ml), the combined org. phases were washed with H_2O, dried, and evaporated. CC on silica gel (pentane) gave 12 mg (10.2%) of a 4:1 mixture of (*Z*)- and (*E*)-isomers (GC). It was purified by treatment with 4-phenyl-1,2,4-triazoline-3,5-dione as described for (+)-**6**. A second CC on silica gel (pentane) yielded 7.56 mg of the pure unnatural (−)-**6**. $[\alpha]_{578}^{25} = -231.5°$ ($c = 0.151$, pentane). Spectroscopic data: see [9].

*(−)-(1R,6S)-8-Oxabicyclo[4.3.0]non-3-en-7-one ((−)-**11**).* *cis*-Cyclohexene-4,5-dimethanol (**12**; 2.0 g, 14 mmol) was enzymatically oxidized with HLADH as described for (+)-**3**. Usual workup yielded 0.92 g (48%) of (−)-**11**. A pure sample showed $[\alpha]_{578}^{25} = -67.3°$ ($c = 4.09$, MeOH), $[\alpha]_D^{25} = -81.7°$ ($c = 2.788$, acetone); 95.7% ee with respect to [19]: $[\alpha]_D = -85.4°$ ($c = 2.63$, acetone).

*(+)-(1S,6R)-8-Oxabicyclo[4.3.0]non-3-en-7-one ((+)-**11**).* a) *Enzymatic Saponification of the* meso-*Diester* **9**. By slow stirring, dimethyl *cis*-4-cyclohexene-1,2-dicarboxylate (16.6 g, 0.1 mol) was suspended in phosphate buffer at pH 7.5 (500 ml) followed by addition of pig-liver esterase (10 mg). The pH was maintained at pH 7.5 by continuous titration with 1.0N NaOH from a peristaltic pump. After *ca.* 24 h, the cloudy suspension became clear, and the saponification was terminated by addition of 0.1N NaOH (100 ml). Unreacted material was extracted with Et_2O (2 × 100 ml), and the aq. phase brought to pH 2 with conc. HCl. Following extractive workup (3 × 100 ml Et_2O), drying, and evaporation, 12.8 g (84.2%) of crude (+)-**10** were obtained. $[\alpha]_{578}^{25} = +14.8°$ ($c = 1.555$, $CHCl_3$), ([26]: $[\alpha]_D = +14.10°$, $CHCl_3$).

b) *Reduction and Lactonization of (+)-**10**.* A soln. of crude (+)-**10** (12.8 g, 0.084 mol) in dry EtOH (70 ml) was slowly added with stirring to Na (5.8 g, 0.25 mol) in liq. NH_3 (500 ml) at −60°. When the dark blue soln. decolorized, another portion of Na (5.8 g, 0.25 mol) was added and stirring continued for 2 h. Excess of Na was destroyed by slow addition of NH_4Cl (0.5 mol) and the NH_3 allowed to evaporate. The residue was dissolved in ice/H_2O (500 ml) and acidified to pH 2 with conc. HCl. The resulting (+)-**11** was extracted with Et_2O (3 × 100 ml), and the combined org. layers were dried and evaporated. Distillation (70°/0.04 Torr) afforded 8.2 g (58% overall)

of (+)-**11**. $[\alpha]_{578}^{25} = 55.6°$ ($c = 1.92$, $CHCl_3$), $[\alpha]_D^{25} = 74.6°$ ($c = 1.92$, acetone; [19]: $[\alpha]_D = +85.2°$, acetone), corresponding to 87.6% ee.

*(−)-(1S,6S)-6-Vinyl-3-cyclohexene-1-methanol ((−)-***13***).* At −70°, 10.7 ml (18.8 mmol) of a 25% soln. of DIBAH in dry toluene (fresh solns. of DIBAH are mandatory!) were added with stirring to a soln. of (+)-**11** (2.0 g, 15 mmol) in 7 ml of dry toluene. The reaction was followed by GC. After complete reduction (*ca.* 45 min), the excess of DIBAH was decomposed by dry CH_3OH (300 µl). After ceasing of the gas evolution, the soln. was poured into a soln. of methylidene(triphenyl)phosphorane in dry THF (30 mmol in 70 ml of dry THF; BuLi as base). Stirring was continued over night at r.t. Then the mixture was poured onto crushed ice/HCl and the aq. phase carefully extracted with Et_2O (3 × 70 ml). The combined org. layers were washed with brine (2 × 50 ml) and H_2O (50 ml), dried, and evaporated. The residue was purified by CC on silica gel (pentane/Et_2O 80:20). Removal of solvent yielded 1.3 g (67%) of pure (−)-**13**. $[\alpha]_{578}^{25} = -15.0°$ ($c = 1.57$, CH_2Cl_2). Spectroscopic data: see [18].

*(+)-(1R,6R)-6-Vinyl-3-cyclohexene-1-methanol ((+)-***13***).* As described, (−)-**11** (1.85 g) was converted into (+)-**13**: 1.37 g (75%). $[\alpha]_{578}^{25} = +16.4°$ ($c = 2.07$, CH_2Cl_2).

*(+)-(1S,6S)-6-Vinyl-3-cyclohexene-1-carbaldehyd ((+)-***14***; cis).* As described for (+)-**6**, (−)-**13** (1.2 g, 8.7 mmol) in CH_2Cl_2 (20 ml) was oxidized with PCC. Usual workup and CC on silica gel (pentane/Et_2O 9:1) yielded 0.95 g (80%) of (+)-**14**. $[\alpha]_{578}^{25} = +73.8°$ ($c = 1.62$, CH_2Cl_2). Spectroscopic data: see [18].

*(−)-(1R,6R)-6-Vinyl-3-cyclohexene-1-carbaldehyd ((−)-***14***; cis).* As above, (+)-**13** (1.5 g, 10.9 mmol) was oxidized to (−)-**14**: 1.18 g (80%). $[\alpha]_{578}^{25} = -80.8°$ ($c = 1.788$, CH_2Cl_2).

*(−)-(1R,6S)-6-Vinyl-3-cyclohexene-1-carbaldehyd ((−)-***15***; trans).* By addition of KOH (50 mg) (+)-**14** (0.9 g, 6.6 mmol) in boiling CH_3OH (25 ml) was epimerized. The progress of the reaction was monitored by GC. The isomerization came to equilibrium after 45 min (62% conversion). Following removal of solvent, the crude aldehydes were redissolved in Et_2O (70 ml), washed with H_2O (20 ml), dried, and chromatographed on silica gel (pentane/Et_2O 9:1): 0.72 g (80%) of (−)-**15**/(+)-**14** (60.4:39.6 (GC)). $[\alpha]_{578}^{25} = -44.0°$ ($c = 1.43$, CH_2Cl_2). Based on the known isomer composition and $[\alpha]_{578}^{25}$ of the *cis*-aldehyde (+)-**14**, the value for the *trans*-isomer (−)-**15** is calculated to $[\alpha]_{578}^{25} = -121.6°$. Spectroscopic data: see [18].

*(+)-(1S,6R)-6-Vinyl-3-cyclohexene-1-carbaldehyd ((+)-***15***; trans).* As above, (−)-**14** (1.0 g, 7.4 mmol) was epimerized with KOH to give 0.7 g (70%) of (+)-**15**/(−)-**14** (63.1:36.9 (GC)). $[\alpha]_{578}^{25} = +50.6°$ ($c = 1.501$, CH_2Cl_2). The value calculated for pure *trans*-isomer (+)-**15** is $[\alpha]_{578}^{25} = +127.4°$.

*(+)-1,1-Dibromo-2-((1R,6S)-6-vinyl-3-cyclohexenyl)ethylene ((+)-***16***; trans).* To a cooled soln. (−10°) of (−)-**15**/(+)-**14** (3:2) (1.36 g, 0.01 mol) and triphenylphosphane (5.24 g, 0.02 mol) in dry CH_2Cl_2 (30 ml) was added with stirring CBr (4.0 g, 0.011 mol) in dry CH_2Cl_2 (10 ml). The soln. turned yellow; stirring was continued at r.t. for 1 h during which a white precipitate separated. Pentane (100 ml) was added and the precipitate removed by suction. The soln. was concentrated and the residue purified by CC on silica gel with pentane. Removal of the solvent yielded 1.29 g (61%) of a colorless heavy oil. A pure sample consisting of 58.8% of *trans*-((+)-**16**) and 41.2% of *cis*-isomer (GC) showed an $[\alpha]_{578}^{25} = +8.8°$ ($c = 2.09$, CH_2Cl_2). IR (neat): 3080, 3030, 2980, 2910, 2830, 1640, 1435, 995, 920, 835, 775, 665. ^{1}H-NMR (CCl_4): (+)-**16**: 1.60–2.65 (*m*, 6H); 4.85–5.2 (*m*, 2H); 5.2–6.15 (*m*, 1H); 5.68 (br. *m*, 2H); 6.22 (*d*, $J = 9$, 1H); deviating resonances of the *cis*-isomer: 2.65–3.0 (*m*, 1H; tert. CH), 6.33 (*d*, $J = 9.5$, 1H). MS (70 eV): 292 (0.04, M^+), 251 (3), 238 (7), 169, 170, 171, 172 (5), 157, 159 (23), 131 (57), 91 (100), 78 (82), 77 (97), 65 (27), 51 (41), 39 (46). Anal. calc. for $C_{10}H_{12}Br_2$ (292.02): C 41.13, H 4.14; found: C 40.95, H 4.20.

*(−)-1,1-Dibromo-2-((1S,6R)-6-vinyl-3-cyclohexenyl)ethylene ((−)-***16***; trans).* As above, (+)-**15**/(−)-**14** (*ca.* 3:2) (1.0 g, 7.4 mmol) was converted to (−)-**16**/*cis*-isomer. After purification, 1.02 g (65%) of (−)-**16**/*cis*-isomer, showing an $[\alpha]_{578}^{25} = -7.02°$ ($c = 4.0$ CH_2Cl_2), were obtained. GC: 64.2% *trans* ((−)-**16**) and 35.8% *cis*.

*(−)-(4R,5S)-4-(1-Propyn-1-yl)-5-vinylcyclohexene ((−)-***17***; trans).* A soln. of (+)-**16**/*cis*-isomer (0.5 g, 2.4 mmol) in dry THF (5 ml) and 1,3-dimethyl-2-imidazilidinone (DMEU; 2 ml) was cooled to −78°, and 5.2 ml of 1M BuLi/hexane was slowly added with stirring. After 45 min, CH_3I (0.98 g, 7.2 mmol) was added and the cooling bath removed. When the soln. had come to r.t., stirring was continued under reflux for further 30 min. The cooled soln. was poured into pentane (100 ml) and washed with dil. HCl (2 × 20 ml), aq. Na_2CO_3 (sat., 2 × 20 ml), and H_2O (1 × 20 ml). After drying and evaporation of solvent, the crude product was purified by CC on silica gel (pentane/Et_2O, 95/5 v/v): 0.2 g (57%) of an inseparable mixture (−)-**17** (*trans*)/*cis*-isomer. $[\alpha]_{578}^{25} = -12.3°$ ($c = 0.175$, CH_2Cl_2). IR (neat): 3080, 3025, 2970, 2920, 2895, 2840, 1640, 1435, 1265, 995, 915, 790, 665. ^{1}H-NMR (CCl_4): (−)-**17**: 1.72 (*d*, $J = 1.5$, 3H); 1.70–2.50 (*m*, 6H); 4.95 (*dd*, $= 9$, 1.5, 1H); 5.00 (*dd*, $J = 15.6$, 1, 1H); 5.55 (br. *m*, 2H); 5.3–6.1 (*m*, 1H); in addition for *cis*-isomer, 2.62 (br. *m*, 1H, *tert.* CH). MS (70 eV): 146 (0.2, M^+), 145 (2.3), 131 (35), 117 (12), 105 (10), 91 (100), 79 (28), 77 (31), 65 (19), 53 (15), 51 (18), 41 (13), 39 (33). Anal. calc. for $C_{11}H_{14}$ (146.23): C 90.35, H 9.65; found: C 90.38, H 9.71.

*(+)-(4S,5R)-4-(1-Propyn-1-yl)-5-vinylcyclohexene ((+)-***17***; trans).* As described for (−)-**17**, from 0.9 g (4.2 mmol) of (−)-**16**/*cis*-isomer: 0.397 g (64%). $[\alpha]_{578}^{25} = +11.4°$ ($c = 0.834$, pentane).

*(−)-(4S,5S)-4-((1E)-1-Propenyl)-5-vinylcyclohexene ((−)-***18***).* At −70°, (−)-**17**/*cis*-isomer (0.2 g, 1.37 mmol) in dry Et_2O (5 ml) was added to liq. NH_3 (50 ml), and finely cut Na (70 mg, 3.0 mmol) was introduced with stirring. Following complete reduction (*ca.* 1.5 h; GC control), excess of Na was destroyed by addition of NH_4Cl (0.2 g, 3.7 mmol). The NH_3 was allowed to evaporate and the residue taken up in H_2O (10 ml) and extracted with pentane (2 × 10 ml). After drying and evaporation of the solvent and purification on silica gel with pentane, isomerically pure (−)-**18** was obtained after CC on silver-impregnated silica gel (10%; *w/w*) using a pentan/Et_2O gradient: 57 mg (25% overall). $[\alpha]_{578}^{25} = -51.2°$ (*c* = 0.505, pentane). Anal. data: see [18].

*(+)-(4R,5R)-4-((1E)-1-Propenyl)-5-vinylcyclohexene ((+)-***18***).* As above, (+)-**17**/*cis*-isomer (0.12 g, 6.84 mmol) was converted into natural (+)-**18**: 21 mg (21% overall). $[\alpha]_{578}^{25} = +54.8°$ (*c* = 0.721, pentane).

Kinetically Controlled Reduction of Racemic Aldehydes rac-**5a** *and* rac-**15** *with HLADH; General Procedure.* EtOH (2.0 ml) was added to a magnetically stirred suspension of NAD^+ (0.5 g) and *rac*-**5a** [9] (2.0 g, 13.5 mmol) or *rac*-**15** [18] (2.0 g, 13.3 mmol) in 200 ml of 0.1M phosphate buffer at pH 7 (3.1 g of KH_2PO_4 in 200 ml of H_2O, adjusted to pH 7 with conc. NaOH). The reduction was started by addition of HLADH suspension (0.5 ml), corresponding to 5 mg of enzyme. The reduction was followed by GC of Et_2O extracts. After a short lag (2–15 min), the reduction proceeded rapidly, and 50% conversion was usually achieved within 30–90 min. At this point, the aq. suspension was extracted with Et_2O (3 × 80 ml). After drying and evaporation, a crude alcohol/aldehyde mixture (−)-**5**/(+)-**5a** and (+)-**13a**/(−)-**15**, resp., was obtained, which could each be easily separated by CC on silica gel using a pentane/Et_2O gradient. In the case of (−)-**5**/(+)-**5a**, only (−)-**5** was obtained, since the very sensitive aldehyde (+)-**5a** did not withstand the chromatographic conditions.

Optical Rotations of Compounds Obtained via *Kinetic Resolution of* rac-**5a** *and* rac-**15**. (−)-(1*S*,2*S*)-**5**: Conversion 60%. Yield 38%. $[\alpha]_{578}^{25} = -156.9°$ (*c* = 0.800, CH_2Cl_2); 73.2% ee as to (+)-**5**.

(−)-(3*S*,4*R*)-**6**: Yield 17%. $[\alpha]_{578}^{25} = -164.4°$ (*c* = 0.221, CH_2Cl_2); 71% ee.

(+)-(1*S*,6*R*)-**13a**: Conversion 47%. Yield 93.8%. $[\alpha]_{578}^{25} = +73.9°$ (*c* = 1.702, CH_2Cl_2); 67% ee (determined after oxidation to the aldehyde (+)-**15**).

(−)-(1*R*,6*S*)-**15**: Yield 90%. $[\alpha]_{578}^{25} = -80.38°$ (*c* = 3.110, CH_2Cl_2); 60.4% ee.

(+)-(1*S*,6*R*)-**15**: Yield 67%. $[\alpha]_{578}^{25} = +89.21°$ (*c* = 1.796, CH_2Cl_2); 67.0% ee.

(+)-(1*R*,6*S*)-**16**: Yield 62%. $[\alpha]_{578}^{25} = +3.42°$ (*c* = 2.342, CH_2Cl_2).

(−)-(1*S*,6*R*)-**16**: Yield 61%. $[\alpha]_{578}^{25} = -3.47°$ (*c* = 2.751, CH_2Cl_2).

(+)-(4*S*,5*R*)-**17**: Yield 64%. $[\alpha]_{578}^{25} = +102.75°$ (*c* = 1.078, CH_2Cl_2).

(−)-(4*R*,5*S*)-**17**: Yield 52%. $[\alpha]_{578}^{25} = -96.08°$ (*c* = 1.197, CH_2Cl_2).

(+)-(4*R*,5*R*)-**18**: Yield 40%. $[\alpha]_{578}^{25} = +34.8°$ (*c* = 1.204, pentane).

(−)-(4*S*,5*S*)-**18**: Yield 39%. $[\alpha]_{578}^{25} = -33.4°$ (*c* = 1.022, pentane).

Chromatographic Separation of Viridiene Enantiomers. A stainless-steel column (25 × 0.4 cm) was slurry-packed with triacetylated cellulose (*CEL AC-40 XF, Macherey and Nagel,* Düren, FRG) according to [25]. The column was equilibrated with EtOH/H_2O 4:1 (flow rate 0.3 ml/min^{-1}) for 2 h, and 20-µl samples of **6** in abs. EtOH (200 ppm) were injected at r.t. The eluant was monitored photometrically at 230 nm corresponding to the absorption maximum of **6** (λ_{max} = 230 nm, ε = 30000). Racemic **6** showed near base-line separation, separation factor α = 1.6. Synthetic (+)- or (−)-**6** eluted as single homogeneous peaks essentially free from mutual contaminations. To determine the detection limit, samples containing 1.5, 3, and 6% of the opposite enantiomer were injected and analyzed quantitatively. Since already admixtures of 1.5% gave distinct signals, the optical purity of the synthetic viridienes had to be > 98.5%. Aucantene (**18**) did not separate under the various conditions employed (*e.g.* solvent composition and temp.).

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