58. Absolute Configuration and Synthesis of (+)-Caudoxirene, the Gamete-Releasing and Gamete-Attracting Pheromone of the Brown Alga *Perithalia caudata* (Phaeophyceae)

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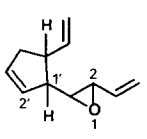
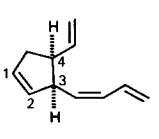
The absolute configuration of the gamete-releasing and -attracting pheromone 2-vinyl-3-(5′-vinylcyclopent-2′-enyl)oxirane (= (+)-caudoxirene; (+)-**1**) of the marine brown alga *Perithalia caudata* is established as (2*R*,3*R*,1′*S*,5′*S*). Highly diastereoselective syntheses and the biological activities of three diastereoisomers of **1** are described. Compound (+)-(2*R*,3*R*,1′*S*,5′*S*)-**1** is the first fully characterized epoxypheromone from marine brown algae (Phaeophyceae).

Introduction. – During sexual reproduction, fertile female gametes of the marine brown alga *Perithalia caudata* release caudoxirene (**1**) as a specific chemical messenger. The signal is secreted together with two inactive by-products, namely viridiene (**2**, *ca.* 4%) and multifidene (**3**, *ca.* 8%) [1] [2] (*Scheme 1*). Caudoxirene (**1**) triggers a cascade of events that culminate in the fusion of the male and female cells forming a zygote. Upon

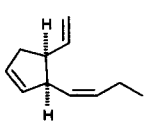
Scheme 1



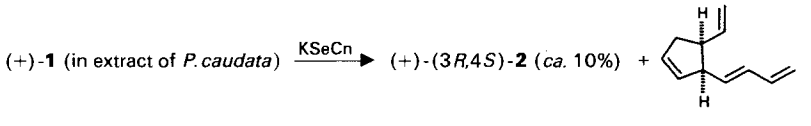
1 caudoxirene



2 viridiene ((+)-(3*R*,4*S*)-**2** shown)



3 multifidene ((3*S*,4*S*)-**3** shown)



(+)-(3*R*,4*S*)-**4** (*ca.* 90%)

contact with ripe antheridia, **1** induces within *ca.* 30 s the discharge of spermatozoids. The motile microgametes then follow the gradient of the pheromone trail towards the egg cell and fertilization takes place. Data regarding the intrinsinc efficiency of the chemotactic response are not available. The obligatory function of caudoxirene (**1**) for sperm release implies that pheromone-free spermatozoids can not be obtained for chemotaxis

bioassays. Temperature shocks which worked well in the case of the brown alga *Laminaria digitata* [3] do not induce sperm release in *P. caudata*. Previous bioassays with synthetic (±)-**1** indicated that the lowest effective concentration for gamete-release is *ca.* 10–100 pmol/l of seawater [1] [2]. These data and the fast response of the signal system of *P. caudata* fit well the findings for other communication systems of brown algae [4] [5].

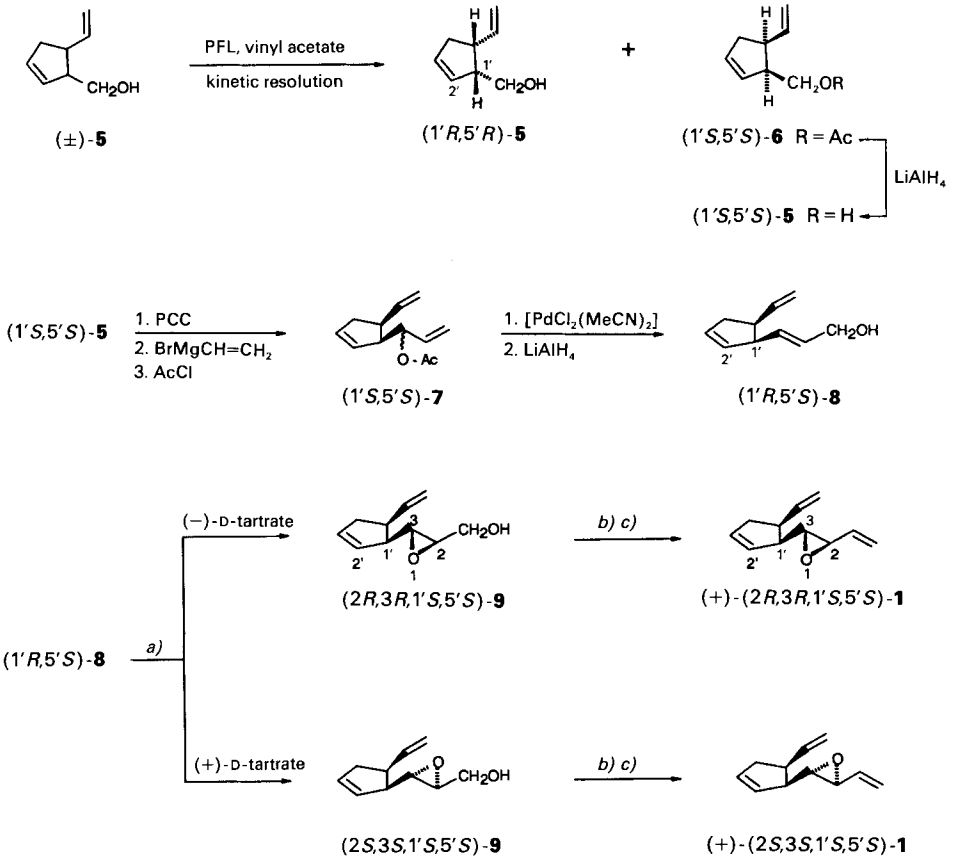
However, in contrast to the well documented absolute configuration(s) and optical purities of the hitherto examined $C_{11}H_{14}$ or $C_{11}H_{16}$ signal molecules like **2** or **3**, respectively, nothing is known about the absolute configuration or diastereoisomeric purity of caudoxirene (**1**). We already showed that gas chromatography (GLC) using modified cyclodextrins as the chiral stationary phases is the method of choice for the enantiomer separation of many algal pheromones. If optically active references are available, the absolute configuration and the *ee* of the natural products can be directly determined from the chromatographic approach. Moreover, the biological activity of the various diastereoisomers of epoxide **1** is unknown, and their evaluation is another important aspect which requires synthetic material. The present work describes the synthesis of some highly pure diastereoisomers of **1** and their application in the evaluation of the absolute configuration of the natural caudoxirene by chromatographic methods. Biological activity tests support the results of the chromatographic/synthetic approach.

Results and Discussion. – *Configurational Assignment of the Cyclopentene Framework of* **1**. Unfortunately, the absolute configuration of the C-framework of caudoxirene (**1**) is not directly accessible by GLC on chiral stationary phases, since synthetic (±)-**1** either fails to separate or decomposes on the employed coatings. But the problem is readily by-passed by deoxygenation of **1** using KSeCN as described previously [2] [6]; the procedure converts (±)-**1** into viridiene ((±)-**2**, 10%) and its (*E*)-isomer (±)-**4** (90%) [7] (see *Scheme 1*). The enantiomers of both olefines can be readily separated by GLC (base-line separation: $\alpha = 1.02$ and 1.035, respectively) using permethyl-α-cyclodextrin as the chiral stationary phase. Since (3*R*,4*S*)- and (3*S*,4*R*)-**2** are known [8], their order of elution can be immediately correlated with their absolute configuration. One antipode of the major product (±)-**4** is available from synthetic (1*R*,2*R*,1′*S*,5′*S*)-**1** by deoxygenation (*vide infra*).

If now combined extracts of *Perithalia caudata*, containing *ca.* 150 μg of caudoxirene (**1**), are subjected to a microscale deoxygenation (3*R*,4*S*)-**4** (92%) and (3*R*,4*S*)-**2** (8%) are found as the only products (> 98% *ee*, each). As the deoxygenation of oxiranes with KSeCN is a stereospecific process (double inversion, followed by extrusion of Se from an episelenide [6] [9]), the production of the small amount of viridiene (**2**; *ca.* 5–10% per run) from configurationally pure caudoxirene (**1**) is most likely due to a subsequent isomerization of the primary product **4** by selenium radicals.

Syntheses. Our synthetic protocol is dictated by the need for an optional access to several configurationally pure diastereoisomers of **1**. This demand is perfectly matched by the combination of the enzyme-mediated resolution of the racemic alcohol (±)-**5** with the *Sharpless* epoxidation of the optically active (*E*)-propenols **8** [10]. In principal, this approach can be exploited for the synthesis of all four diastereoisomers of **1**. The acylation of (+)-**5** is best achieved with a lipase from *Pseudomonas fluorescens* (PFL) using vinyl acetate as the solvent and irreversible acyl donor. At low conversion rate (45%), acetate (1′*S*,5′*S*)-**6** is obtained with very high optical purity (> 98% *ee*), while at

Scheme 2



a) *Sharpless* epoxidation. *b*) PCC. *c*) CH_2=P(Ph)$_3$.

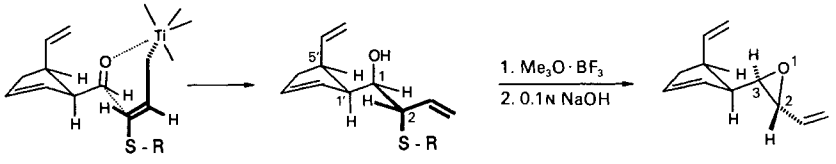
55% conversion of (±)-**5**, the unreacted alcohol (1'*R*,5'*R*)-**5** is of very high purity (> 98% *ee*) [11]. Reductive removal of the acetate gives (1'*S*,5'*S*)-**5**.

Alcohol (1'*S*,5'*S*)-**5** (or (1'*R*,5'*R*)-**5**) is readily oxidized with pyridinium chlorochromate (PCC) to the corresponding aldehyde. However, the latter is rather unstable and, due to rapid enolization of only limited use for alkylation reactions [12]. *E.g.*, the aldehyde fails to give defined products with either stabilized or non-stabilized phosphonium- or arsonium ylids which could be used for a straightforward elaboration of the C_4-side chain [13]. This is exemplified by the reaction of the aldehyde with (propenylidene)triphenylarsorane which leads to a complex mixture of *cis*/*trans*-caudoxirenes (rel. to oxirane) and (*E*/*Z*)-viridienes **2**/**4**, along with a great number of unidentified products. On the other hand, weakly basic, but highly nucleophilic and coordinating reagents like alkynyl- or alkenylmagnesium and -titanium reagents can be used for this purpose [2]. Thus, treatment of the crude aldehyde (the compound decomposes during purification on SiO_2) obtained from (1'*S*,5'*S*)-**5** with vinylmagnesium bromide, followed by addition of

AcCl gives (1′*S*,5′*S*)-**7**. The only moderate overall yield (28%) can not be increased by application of the corresponding organocerium reagent [14]. In the presence of the electrophilic $[PdCl_2(MeCN)_2]$ the diastereoisomeric acetates (1*S*,5′*S*)-**7** undergo a facile [3,3]-sigmatropic rearrangement [15] leading to an equilibrium mixture containing *ca.* 80% of the sterically less demanding terminal acetate; reductive deacetylation yields (1′*R*,5′*S*)-**8** (> 97% (*E*)-isomer). Competing interactions by the other double bonds do not occur, provided that the reaction is carried out at room temperature. Subsequent asymmetric epoxidations with (+)-L- or (−)-D-dimethyl tartrate as chiral auxiliary proceed without difficulty. In agreement with the well documented stereochemical course of this reaction with simple (*E*)-alkenols, *Si*-attack of the double bond of (1′*R*,5′*S*)-**8** is preferred with (−)-D-tartrate [10], and (2*R*,3*R*,1′*S*,5′*S*)-**9** is produced as the major product (96% *de* according to GLC). The same reaction with (+)-L-tartrate gives (2*S*,3*S*,1′*S*,5′*S*)-**9** (97% *de* by GLC). Following separation and final oxidation with PCC and *Wittig* reaction with (methylidene)triphenylphosphorane, the diastereoisomeric oxiranes (+)-(2*R*,3*R*,1′*S*,5′*S*)- and (+)-2*S*,3*S*,1′*S*,5′*S*)-**1**, respectively, are obtained. Due to the ease of the GLC separation of these two diastereoisomers, the absolute configuration of the oxirane moiety of the natural pheromone can be immediately correlated with (+)-(2*R*,3*R*,1′*S*,5′*S*)-**1**, the product of the epoxidation of (1′*R*,5′*S*)-**8** with unnatural (−)-D-dimethyl tartrate (*Kovàts* indices; *cf. Exper. Part*).

In contrast to the highly versatile, but low-yielding route of *Scheme 2*, the strategy of *Scheme 3* is much more effective. In agreement with the models of *Cram* [16] or *Felkin-Anh* [17], the bulky organotitanium reagents **10** add to the least hindered π-face of the carbonyl compound derived from alcohols (1*R*′,5′*R*)- or (1′*S*,5′*S*)-**5**. The 2-(phenylthio)butenol **11a** ((1*R*,2*S*,1′*S*,5′*S*)) is formed with high purity (94% *de* by GLC).

Scheme 3



Aldehyde from (1′*S*,5′*S*)-**5** **10a** R = Ph **11a** R = Ph, (1*R*,2*S*,1′*S*,5′*S*) (+)-(2*R*,3*R*,1′*S*,5′*S*)-**1**
b R = Et (**11b** R = Et, (1*S*,2*R*,1′*R*,5′*R*)[a]) ((−)-(2*S*,3*S*,1′*R*,5′*R*)-**1**[a])

a) *Formula* not shown.

Subsequent alkylation with $Me_3O \cdot BF_4$ and base-induced intramolecular displacement of the resulting sulfonium salt can be carried out in a single operation and provides (+)-(2*R*,3*R*,1′*S*,5′*S*)-**1**, identical with the natural pheromone, in 40% overall yield from **11a** [2]. Repetition of the sequence with (1′*R*,5′*R*)-**5** yields *via* **11b** the unnatural (−)-(2*R*,3*R*,1′*R*,5′*R*)-**1**.

Biological Activity of the Diastereoisomeric Caudoxirenes. – For gamete release, decadic dilution series (1 mmol→1 nmol) of (+)-(2*R*,3*R*,1′*S*,5′*S*)-, (+)-(2*S*,3*S*,1′*S*,5′*S*)-, and (−)-(2*R*,3*R*,1′*R*,5′*R*)-**1** are prepared in *FC 72* (fluorocarbon, *3M Company*, Düsseldorf, FRG). Microdroplets of *ca.* 0.3 μl are placed in a depression slide in close vicinity to

mature male gametophytes of *Perithalia caudata*. At active pheromone concentrations, release of spermatozoids occurs within *ca.* 30 s. The actual concentration of caudoxirene in the aqueous interphase is calculated from the lowest effective concentration of the respective caudoxirene diastereoisomer in the organic phase (*FC 72*) using the experimentally determined partition coefficient ($K_{FC\ 72/seawater} = 21 \pm 2.5$) [2]. In agreement with the anal. data (*vide supra*), the most effective compounds is (+)-(2*R*,3*R*,1′*S*,5′*S*)-**1** (> 97% *de*) which is able to trigger the gamete-release at 50 pmol/l seawater. If the spatial arrangement of the substituents at the cyclopentene ring is inverted, while the configuration at the oxirane are retained (see (−)-(2*R*,3*R*,1′*R*,5′*R*)-**1**; 96% *de*), the release of spermatozoids requires a 100-fold concentration increase (threshold: 5 nmol/l seawater). Inversion of the configuration at the oxirane moiety in combination with the natural arrangement of the substituents at the cyclopentene ring (see (+)-(2*S*,3*S*,1′*S*,5′*S*)-**1**) has the same effect (threshold: 5 nmol/seawater).

It is worth to mention that the absolute configuration and high optical purity of the C-framework of (+)-caudoxirene ((+)-(2*R*,3*R*,1′*S*,5′*S*)-**1**) fits well with the structural aspects of all other cyclopentenoid pheromones, release factors, or even by-products of marine brown algae (*cf.* viridiene (**2**) or multifidene (**3**)) [18]. Moreover, the same activity difference (100-fold) was observed for the natural and nonnatural enantiomers of multifidene, (+)- and (−)-**3**, respectively, as a release factor for spermatozoids of the brown alga *Chorda tomentosa* [19]. Another 100-fold activity difference between the two enantiomers of **2** or **3** (> 98% *ee*, each) was found with respect to their chemotactic potential for spermatozoids [18]. It remains to be clarified, whether these coincidences simply reflect the optical purities of the nonnatural enantiomers of multifidene (**3**), viridiene (**2**; > 98% *ee*, each), and the diastereoisomers of caudoxirene (**1**; > 96% *de*, each), or whether they reflect the intrinsic activity of the unnatural compounds.

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Experimental Part

General. Reactions are performed under Ar. Solvents and reagents are purified and dried prior to use. Anh. $MgSO_4$ is used for drying operations. Solns. are usually concentrated by flash evaporation under reduced pressure. Anal. TLC: 20 × 20 cm TLC plates, SiO_2 *60* F_{254}, layer thickness 0.2 mm (*Macherey & Nagel*, D–5160 Düren). Anal. GLC: *Carlo-Erba* gas chromatograph, *HRGC 5300* equipped with fused-silica capillaries coated with *SE 30* (10 m × 0.31 mm), *Carbowax* (30 m × 0.25 mm), or permethyl-α-cyclodextrin (50 m × 0.25 mm), Fa. *K. Ziemer*, D–6800 Mannheim; H_2 at 30 cm/s as carrier gas. Polarimetry: *Perkin-Elmer-241* polarimeter. IR (cm^{-1}): *Perkin-Elmer-882* IR spectrophotometer. ^{1}H-NMR (250 or 400 MHz, $CDCl_3$, TMS as internal standard): *Bruker Cryospec WM 250* and *Bruker WM 400*. MS (*m/z*): *Finnigan MAT 90* and *Finnigan ITD 800* combined with a *Carlo Erba* gas chromatograph, model *Vega*; He at 30 cm/s as carrier gas.

*(+)-(1′*R*,5′*S*,2*E*)-3-(5′-Vinylcyclopent-2′-enyl)prop-2-en-1-ol* ((1′*R*,5′*S*)-**8**). A soln. of (1′*S*,5′*S*)-**7** [11] (2.49 g, 13.0 mmol) and $[PdCl_2(MeCN)_2]$ (300 mg, 1.16 mmol) in dry THF (40 ml) is stirred at r.t. for 3 d. The yellow soln. is diluted with Et_2O (150 ml), washed with H_2O (50 ml) and brine (50 ml), and dried. After evaporation, the crude product is reduced with $LiAlH_4$ (0.87 g, 23 mmol) at 0° in dry Et_2O (100 ml). Hydrolysis with 2N HCl (100 ml), extractive workup (3 × 70 ml Et_2O), and CC (silica gel, pentane/Et_2O 90:10) afford (1′*R*,5′*S*)-**8** (1.12 g, 56%). Colorless, viscous oil. $[\alpha]_{578}^{25} = +352.2$ (*c* = 3.01, CH_2Cl_2). IR (neat): 3323v*s*, 3057*s*, 3005*m*, 2980*s*, 2905v*s*, 2846v*s*, 1666*w*, 1638*m*, 1609*w*, 1443*m*, 1420*s*, 1370*m*, 1299*m*, 1091*s*, 1002v*s*, 993v*s*, 974v*s*, 911v*s*, 797v*s*, 724v*s*. ^{1}H-NMR

($CDCl_3$): 5.89–5.74 (*m*, CH_2=C*H*, H–C(2′ or 3′)); 5.68–5.48 (*m*, H–C(2), H–C(3), H–C(2′ or 3′)); 5.05–4.95 (*m*, CH_2=CH); 4.09 (*d*, *J* = 5.0, 2H–C(1)); 3.33 (*t*, *J* = 7.7, H–C(1′)); 2.99 (*quint.*, *J* = 8.2, H–C(5′)); 2.44 (*dd*, *J* = 8.1, 8.1, 1H–C(4′)); 2.31–2.18 (*m*, 1H–C(4′)); 1.48 (OH). ^{13}C-NMR ($CDCl_3$): 140.0 (CH_2=*C*H); 133.2 (C(2′ or 3′)); 132.4 (C(2)); 103.8 (C(2′ or 3′)); 129.3 (C(3)); 114.4 (*C*H=CH); 63.6 (C(1)); 51.3 (C(1′)); 46.9 (C(5′)); 37.1 (C(4′)). MS (70 eV): 132 (2, $[M - H_2O]^{+\cdot}$), 131 (4), 119 (8), 117 (22), 115 (10), 106 (13), 105 (8), 104 (13), 92 (12), 91 (100), 81 (12), 79 (63), 78 (28), 77 (49), 67 (26), 66 (34), 65 (29), 63 (13), 55 (17), 53 (21), 51 (27), 50 (16), 43 (19), 41 (51), 40 (13), 39 (83), 38 (13). HR-MS: 132.0932 ($C_{10}H_{12}$, $[M - H_2O]^{+\cdot}$, calc. 132.09390).

*(+)-(2*R*,3*R*,1′*S*,5′*S*)-3-(5′-Vinylcyclopent-2′-enyl)oxirane-2-methanol* ((2*R*,3*R*,1′*S*,5′*S*)-**9**). To a cold soln. (−22°) of (−)-D-dimethyl tartrate (2.09 g, 11.7 mmol) in dry CH_2Cl_2 (30 ml) is gradually added with stirring $Ti(i\text{-}PrO)_4$ (2.86 g, 10.1 mmol). The complex is aged for 30 min, and a soln. of (1′*R*,5′*S*)-**8** (0.502 g, 3.35 mmol; > 98% *ee*) in CH_2Cl_2 (5 ml) is added. Then, the temp. is lowered to −30°, *t*-BuOOH (5.6 ml, 16.8 mmol; 3M soln. in isooctane) added, and stirring continued for 15 h. Et_2O (80 ml) is added and the mixture hydrolyzed with 10% aq. tartaric-acid soln. (100 ml). The aq. layer is separated and extracted with Et_2O (5 × 50 ml). The combined org. layers are washed with H_2O (20 ml) and brine (100 ml), dried, and evaporated. CC (silica gel, pentane/Et_2O 60:40) affords (2*R*,3*R*,1′*S*,5′*S*)-**9** (0.396 g, 71%). Colorless, viscous oil. $[\alpha]_{578}^{25}$ = +237.9 (*c* = 2.01, CH_2Cl_2); 96% *de* by GLC. IR (neat): 3419*vs*, 3061*s*, 2982*s*, 2925*vs*, 2849*s*, 1742*m*, 1637*m*, 1612*w*, 1446*m*, 1420*m*, 1270*m*, 1231*m*, 1085*s*, 1027*s*, 996*s*, 959*m*, 915*vs*, 895*vs*, 808*vw*, 785*vw*, 732*vw*. ^{1}H-NMR ($CDCl_3$): 5.95 (*ddd*, *J* = 17.0, 10.0, 9.0, CH_2=C*H*); 5.89–5.85, 5.75–5.72 (2*m*, H–C(2′), H–C(3′)); 5.10 (*dt*, *J* = 17.1, 1.7, 1H, CH_2=CH); 5.04 (*dd*, *J* = 10.1, 1.7, 1H, CH_2=CH); 3.88 (*dd*, *J* = 12.8, 2.5, 1H, CH_2OH); 3.59–3.54 (*m*, 1H, CH_2OH); 3.06 (*quint.*, *J* = 8.3, H–C(5′)); 2.93–2.90 (*m*, H–C(2)); 2.83 (*dd*, *J* = 7.5, 2.3, H–C(3)); 2.59–2.46 (*m*, 1H–C(4′), H–C(1′)); 2.35–2.27 (*m*, 1H–C(4′)); 2.00 (*t*, *J* = 6.2, OH). ^{13}C-NMR ($CDCl_3$): 140.0 (CH_2=*C*H); 132.6, 130.2 (C(2′), C(3′)); 115.4 (*C*H_2=CH); 61.7 (CH_2OH); 57.9 (C(2)); 56.9 (C(3)); 50.7 (C(1′)); 45.4 (C(5′)); 37.9 (C(4′)). MS (70 eV): 135 (3), 117 (5), 115 (4), 106 (12), 105 (25), 93 (8), 91 (100), 81 (13), 79 (45), 78 (39), 77 (50), 69 (10), 67 (14), 66 (11), 65 (25), 55 (8), 53 (10), 51 (20), 50 (10), 43 (21), 41 (27), 40 (11), 39 (68), 38 (10). HR-MS: 148.0874 ($C_{10}H_{12}O$, $[M - H_2O]^{+\cdot}$, calc. 148.08881).

*(+)-(2*S*,3*S*,1′*S*,5′*S*)-3-(5′-Vinylcyclopent-2′-enyl)oxirane-2-methanol* ((2*S*,3*S*,1′*S*,5′*S*)-**9**). As described above, with (1′*R*,5′*S*)-**8** (450 mg, 2.95 mmol; 97% *ee*) and (+)-L-dimethyl tartrate; 0.36 g (73.3%) $[\alpha]_{578}^{25}$ = +304.6 (*c* = 1.57, CH_2Cl_2); 97% *de* by GLC. IR (neat): 3433*vs*, 3058*m*, 2980*s*, 2924*vs*, 2847*s*, 1747*m*, 1636*m*, 1610*w*, 1445*m*, 1419*m*, 1233*m*, 1083*s*, 1035*s*, 995*s*, 962*m*, 911*vs*, 897*vs*, 788*w*, 759*m*, 731*s*. ^{1}H-NMR ($CDCl_3$): 6.00 (*ddd*, *J* = 17.1, 10.3, 8.3, CH_2=C*H*); 5.87–5.84, 5.54–5.51 (2*m*, H–C(2′), H–C(3′)); 5.11 (*dt*, *J* = 17.1, 1.5, 1H, CH_2=CH); 5.05 (*dquart.*, *J* = 10.3, 0.9, 1H, CH_2=CH); 3.85 (*dd*, *J* = 12.8, 2.5, 1H, CH_2OH); 3.55 (*dd*, *J* = 12.5, 4.5, 1H, CH_2OH); 3.08 (*quint.*, *J* = 7.3, H–C(5′)); 2.91–2.88 (*m*, H–C(2)); 2.86 (*dd*, *J* = 6.8, 2.3, H–C(3)); 2.77 (*t*, *J* = 7.5, H–C(1′)); 2.50 (*ddt*, *J* = 16.5, 8.3, 2.5, 1H–C(4′)); 2.34–2.26 (*m*, 1H–C(4′)); 2.19 (*s*, OH). ^{13}C-NMR ($CDCl_3$): 139.7 (CH_2=*C*H); 133.0, 129.0 (C(2′), C(3′)); 115.5 (*C*H_2=CH); 61.8 (CH_2OH); 56.6 (C(2)); 55.3 (C(3)); 50.3 (C(1′)); 45.0 (C(5′)); 37.3 (C(4′)). MS (70 eV): 135 (7), 133 (3), 117 (10), 105 (21), 93 (13), 91 (100), 81 (15), 79 (56), 78 (38), 77 (65), 69 (12), 67 (16), 66 (19), 65 (29), 55 (15), 53 (17), 51 (28), 50 (12), 43 (23), 41 (30), 40 (13), 39 (72), 38 (10). HR-MS: 166.0998 ($C_{10}H_{14}O_2$, $M^{+\cdot}$, calc. 166.09938).

*(+)-(2*R*,3*R*,1′*S*,5′*S*)-2-Vinyl-3-(5′-vinylcyclopent-2′-enyl)oxirane* (= (+)-*Caudoxirene*; (+)-(2*R*,3*R*,1′*S*,5′*S*)-**1**). A soln. of (2*R*,3*R*,1′*S*,5′*S*)-**9** (0.196 g, 1.18 mmol; 96% *de*) in dry CH_2Cl_2 (25 ml) is treated with stirring at r.t. with pyridinium chlorochromate (PCC; 0.64 g, 3.0 mmol). After 2 h, pentane (50 ml) and $MgSO_4$ (*ca.* 0.5 g) are added to precipitate the chromium salts. The mixture is filtered and the soln. evaporated. Repetition of the procedure removes last admixtures of the chromium salts. Then, a soln. of the crude aldehyde in dry THF (20 ml) is treated with stirring at r.t. with (methylidene)triphenylphosphorane (5.9 ml, 2.95 mmol; 0.5M in THF). Stirring is continued for 25 min, and then the soln. is diluted with Et_2O (50 ml) and hydrolyzed with 10% aq. tartaric-acid soln. (70 ml). Following extractive workup (2 × 50 ml pentane) and CC (silica gel, pentane/Et_2O 98:2), (2*R*,3*R*,1′*S*,5′*S*)-**1** is obtained as a colorless liquid which is further purified by MPLC (SiO_2): 39.4 mg (20.6% overall). $[\alpha]_{578}^{25}$ = +238.3 (*c* = 1.50, CH_2Cl_2); 90% *de* by GLC. Spectroscopic data: see [2].

*(+)-(2*S*,3*S*,1′*S*,5′*S*)-2-Vinyl-3-(5′-vinylcyclopent-2′-enyl)oxirane* ((+)-(2*S*,3*S*,1′*S*,5′*S*)-**1**). From (2*S*,3*S*,1′*S*,5′*S*)-**9** (0.29 g, 1.75 mmol; 97% *de*) as described above: 44 mg (16% overall). $[\alpha]_{578}^{25}$ = +293.5 (*c* = 1.26, CH_2Cl_2); 88% *de* by GLC. IR (neat): 3058*w*, 2980*m*, 2928*m*, 2847*m*, 1636*m*, 1609*m*, 1446*w*, 1419*w*, 1401*w*, 986*s*, 958*w*, 915*s*, 891*s*, 805*w*, 731*m*. ^{1}H-NMR ($CDCl_3$): 6.00 (*ddd*, *J* = 16.8, 10.2, 8.3, CH_2=C*H*–C(5′)); 5.87–5.85, 5.56–5.54 (2*m*, H–C(2′), H–C(3′)); 5.54 (*ddd*, *J* = 17.2, 10.0, 7.5, CH_2=C*H*–C(2)); 5.43 (*dd*, *J* = 17.2, 1.7, 1H, CH_2=CH–C(2)); 5.23 (*dd*, *J* = 10.2, 1.5, 1H, CH_2=CH–C(2)); 5.11 (*ddd*, *J* = 17.2, 1.5, 1.5, 1H, CH_2=CH–C(5′)); 5.05 (*ddd*, *J* = 10.2, 1.8, 0.8, 1H, CH_2=CH–C(5′)); 3.09 (*quint.*, *J* = 8.0, H–C(5′)); 3.08 (*dd*, *J* = 7.4, 1.6, H–C(2)); 2.79 (br. *t*, *J* = 7.4, H–C(1′)); 2.76 (*dd*, *J* = 6.8, 2.0, H–C(3)); 2.54–2.47, 2.34–2.26 (2*m*, 2H–C(4′)). ^{13}C-NMR: 138.8 (CH_2=*C*H–C(5′)); 135.7 (CH_2=*C*H–C(2)); 132.9, 129.7 (C(2′), C(3′)); 119.0

(CH_2=CH–C(2)); 115.2 (CH_2=CH–C(5')); 59.8 (C(3)); 56.8 (2); 50.9 (C(1')); 45.2 (C(5')); 37.6 (C(4')). MS (70 eV): 121 (2), 119 (2), 117 (3), 106 (10), 105 (18), 92 (10), 91 (100), 79 (35), 78 (51), 77 (44), 66 (12), 65 (26), 55 (11), 51 (19), 41 (28), 40 (13), 39 (91), 38 (15). HR-MS: 162.1024 ($C_{11}H_{14}O$, M^+, calc. 162.10447).

(+)-(1R,2S,1'S,5'S)-2-(Phenylthio)-1-(5'-vinylcyclopent-2'-enyl)but-3-en-1-ol (**11a**). As described in [2], **11a** is prepared from (1'*S*,5'*S*)-**5** (> 98% *ee*): 53% overall. $[\alpha]_{578}^{20}$ = +113.7 (*c* = 6.36, CH_2Cl_2). Spectroscopic data: see [2].

(–)-(1S,2R,1'R,5'R)-2-(Ethylthio)-1-(5'-vinylcyclopent-2'-enyl)but-3-en-1-ol (**11b**). In analogy to the procedure described in [2], **11b** is prepared from (1'*R*,5'*R*)-**5** (> 98% *ee*) using the anion of ethyl allyl sulfide (*t*-BuLi for deprotonation): 37.2% overall. $[\alpha]_{578}^{20}$ = –121.3 (*c* = 4.06, CH_2Cl_2). IR (neat): 3479*s* (br.), 3076*m*, 2977*s*, 2927*s*, 2848*m*, 1834*vw*, 1632*vw*, 1448*w*, 1419*m*, 1376*w*, 1265*m*, 1075*s*, 1044*m*, 994*s*, 913*vs*, 814*w*, 730*m*, 686*m*. ^{1}H-NMR: 6.01 (*ddd*, *J* = 17.3, 10.2, 9.5, CH_2=C*H*); 5.96–5.93, 5.82–5.79 (2*m*, H–C(2'), H–C(3'); 5.80 (*ddd*, *J* = 16.8, 10.0, 9.9, H–C(3)); 5.19 (*dd*, *J* = 10.1, 1.6, 1H–C(4)); 5.11 (*dd*, *J* = 17.0, 1.5, 1H–C(4)); 5.10 (*dt*, *J* = 17.2, 1.0, 1H, CH_2=CH); 5.04 (*dd*, *J* = 10.1, 2.1, 1H, CH_2=CH); 3.69 (*quart.*, *J* = 5.6, H–C(1)); 3.35 (*dd*, *J* = 9.7, 9.7, H–C(2)); 3.07–3.02 (*m*, H–C(1')); 2.95 (*quint.*, *J* = 8.3, H–C(5')); 2.51–2.44 (*m*, 1H–C(4')); 2.46 (*quart.*, *J* = 7.4, CH_3CH_2S); 2.29–2.22 (*m*, 1H–C(4')); 2.01 (*d*, *J* = 5.8, OH); 1.22 (*t*, *J* = 7.4, CH_3CH_2S). ^{13}C-NMR: 139.8 (CH_2=CH); 135.7 (C(3)); 133.1, 129.3 (C(2'), C(3')); 117.4 (C(4)); 115.5 (CH_2=CH); 72.2 (C(1)); 52.8 (C(2)); 51.5 (C(1')); 45.4 (C(5')); 38.9 (C(4')); 24.4 (CH_3CH_2S); 14.6 (CH_3CH_2S). MS (70 eV): 195 ([*M* – Et]$^+$), 145 (53), 131 (10), 117 (23), 103 (20), 102 (100), 101 (20), 95 (20), 93 (39), 91 (79), 79 (47), 77 (62), 74 (38), 73 (61), 69 (27), 65 (34), 59 (45), 55 (22), 53 (22), 51 (20), 45 (61), 41 (73), 39 (97). HR-MS: 224.1197 ($C_{13}H_{20}OS$, M^+, calc. 224.12349).

(+)-(2R,3R,1'S,5'S)-2-Vinyl-3-(5'-vinylcyclopent-2'-enyl)oxirane (= (+)-*Caudoxirene*; (+)-(2*R*,3*R*,1'*S*,5'*S*)-**1**). Prepared from **11a** (0.239 g, 0.88 mmol) as described [2]: 57.0 mg (40%). $[\alpha]_{578}^{20}$ = +239.6 (*c* = 2.64, CH_2Cl_2).

(–)-(2S,3S,1'R,5'R)-2-Vinyl-3-(5'-vinylcyclopent-2'-enyl)oxirane ((–)-(2*S*,3*S*,1'*R*,5'*R*)-**1**). Prepared from **11b** (0.15 g, 0.67 mmol) as described [2]: 78.0 mg (72%). $[\alpha]_{578}^{20}$ = –251.6 (*c* = 3.60, CH_2Cl_2).

(1E)-3-(Buta-1',3'-dienyl)-4-vinylcyclopentene ((±)-**4**): *Prep. Deoxygenation of (±)-Caudoxirene* ((±)-**1**). A soln. of (±)-**1** (75 mg, 0.46 mmol) in Et_2O (5 ml) and a sat. soln. of $(NH_2)_2C$=S in MeOH (10 ml) are combined and refluxed for 3 d. After cooling, the olefins (±)-**4**/(±)-**2** (96:4) are extracted with pentane (2 × 15 ml). Usual workup and CC (*Florisil* (100–200 mesh), pentane) afford (±)-**4** (96%) and (±)-**2** (4%; by GLC). Total yield: 11 mg (16.5% overall). IR ($CDCl_3$): 3060*m*, 3005*m*, 2977*m*, 2928*s*, 2847*m*, 2249*w*, 1704*m*, 1637*m*, 1601*w*, 1441*w*, 1417*w*, 1357*w*, 1257*w*, 1221*w*, 1004*vs*, 950*m*, 923*m*, 764*w*, 677*w*, 654*m*. ^{1}H-NMR ($CDCl_3$): 6.31 (*ddd*, *J* = 17.0, 10.3, 10.3, H–C(3')); 6.03 (*ddd*, *J* = 15.2, 10.4, 0.7, H–C(2')); 5.83–5.80 (*m*, H–C(1 or 2)); 5.82 (*ddd*, *J* = 17.1, 10.2, 8.3, CH_2=C*H*); 5.67–5.64 (*m*, H–(1 or 2)); 5.55 (*dd*, *J* = 15.4, 8.5, H–C(1')); 5.11 (br. *d*, *J* = 17.0, 1H–C(4')); 5.03–4.95 (*m*, CH_2=CH, 1H–C(4')); 3.36 (br. *t*, *J* = 7.5, H–C(3)); 3.00 (*quint.*, *J* = 8.2, H–C(4)); 2.48–2.41, 2.30–2.22 (*m*, 2H–C(5)). ^{13}C-NMR: 140.0 (CH_2=CH); 137.1 (C(3')); 134.7 (C(1')); 133.1 (C(1 or 2)); 130.9 (C(2')); 130.8 (C(1 or 2)); 115.3 (C(4')); 114.4 (CH_2=CH); 51.8 (C(3)); 47.3 (C(4)); 37.2 (C(5)). MS (70 eV): 146 (M^+, 1), 145 (3), 130 (28), 128 (7), 117 (44), 115 (23), 105 (40), 104 (11), 103 (21), 93 (37), 92 (100), 81 (33), 80 (75), 79 (15), 78 (47), 68 (12), 66 (27), 64 (14), 54 (16), 52 (28), 51 (16), 42 (22), 40 (86), 39 (11). HR-MS: 146.1084 ($C_{11}H_{14}$, M^+, calc. 146.10955).

Anal. Deoxygenation of the Perithalia caudata *Extract.* Several samples of enriched volatiles from fertile female gametophytes of *Perithalia caudata* (CH_2Cl_2 as solvent) were combined to give *ca.* 150 µl of a soln. containing *ca.* 150 µg (*ca.* 1 µmol) of natural caudoxirene. This soln. is carefully evaporated to a final volume of *ca.* 5 µl by a gentle stream of air. Then, 80 µl of a KSeCN soln. in MeOH (50 mg/ml, 28 µmol) is added and the sealed tube kept at 67° for 2 h. The resulting mixture (80% conversion; containing (+)-(3*R*,4*S*)-**2** (10%) and (+)-(3*R*,4*S*)-**4** (90%)) can be immediately used for GLC and GLC/MS analyses. The procedure was previously optimized with synthetic material; (*E*/*Z*)-ratios between 92:8 and 85:15 were observed (by GLC).

Determination of the Absolute Configuration and the Enantiomeric Excess (ee) *of the Deoxygenated Products.* Following deoxygenation, the absolute configuration and the *ee* of the C-framework of natural and synthetic samples of caudoxirene **1** can be determined by GLC (fused-silica capillary, coated with permethyl-α-cyclodextrin (50 m × 0.25 mm); column oven 80°). The elution order of the enantiomers is determined using synthetic references of (+)/ and (–)-**2** [20] or (+)-**4**; see above. Results: (+)-**2** and (+)-**4** from caudoxirene (natural), ⩾ 98% *ee*; (+)-**2** and (+)-**4** from (+)-(2*R*,3*R*,1'*S*,5'*S*)-**1** (*via* **11a**), ⩾ 98% *ee*; (–)-**2** and (–)-**4** from (–)-(2*S*,3*S*,1'*R*,5'*R*)-**1** (*via* **11b**), ⩾ 98% *ee*; (+)-**2** and (+)-**4** from (+)-(2*R*,3*R*,1'*S*,5'*S*)-**1** (*via* (2*R*,3*R*,1'*S*,5'*S*)-**9**), ⩾ 98% *ee*; (+)-**2** and (+)-**4** from (+)-(2*S*,3*S*,1'*S*,5'*S*)-**1** (*via* (2*S*,3*S*,1'*S*,5'*S*)-**9**); ⩾ 98% *ee*.

Identification of the Natural Diastereoisomer of Caudoxirene via Kovàts *Indices. Kovàts* indices were determined on an unpolar (*SE 30*, 60°) and on a polar column (*Carbowax*, 120°). Solns. (0.1 mmol each) of (+)-(2*R*,3*R*,1'*S*,5'*S*)-**1** from (2*R*,3*R*,1'*S*,5'*S*)-**9**, of (+)-(2*R*,3*R*,1'*S*,5'*S*)-**1** from **11a**, and of (+)-(2*S*,3*S*,1'*S*,5'*S*)-**1** from

(2*S*,3*S*,1′*S*,5′*S*)-**9**, containing each three neighbouring *n*-alkanes as internal standards, were injected, yielding the following indices (*Carbowax* data in parentheses): 1152.25 ± 0.13 (1583.78 ± 0.13), 1152.01 ± 0.17 (1583.72 ± 0.08), and 1158.57 ± 0.17 (1592.42 ± 0.15), resp. The indices of (+)-**1** from *Perithalia caudata,* 1152.10 ± 0.17 (1583.73 ± 0.10), confirm its absolute configuration to be (2*R*,3*R*,1′*S*,5′*S*).

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