Structures of Zeylenol and Zeylena, Constituents of *Uvaria zeylanica* (Annonaceae)

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From the methanol extract of the roots of *Uvaria zeylanica* (Annonaceae), two new crystalline compounds, named zeylenol and zeylena, have been isolated. Evidence is presented that zeylenol, $C_{21}H_{20}O_7$, a minor constituent, has structure **1a** and that zeylena, $C_{23}H_{20}O_5$, a major constituent, has structure **3a**. Benzene oxide **6** is an apparent biogenetic precursor for these two and many other substances found in *Uvaria* species; its conversion to zeylena (**3a**) involves addition of (*E*)-cinnamic acid followed by an intramolecular Diels–Alder reaction.

During the course of our investigation of the methanol extract of the roots of *Uvaria zeylanica* L. (annonaceae) for tumor inhibitory constituents, two new crystalline compounds, zeylenol (**1a**) and zeylena (**3a**), were encountered (see Chart I). Although both were found inactive in the P-388 lymphocytic leukemia test system, their isolation, characterization, and biogenetic relationship to other *Uvaria* constituents are described herein.

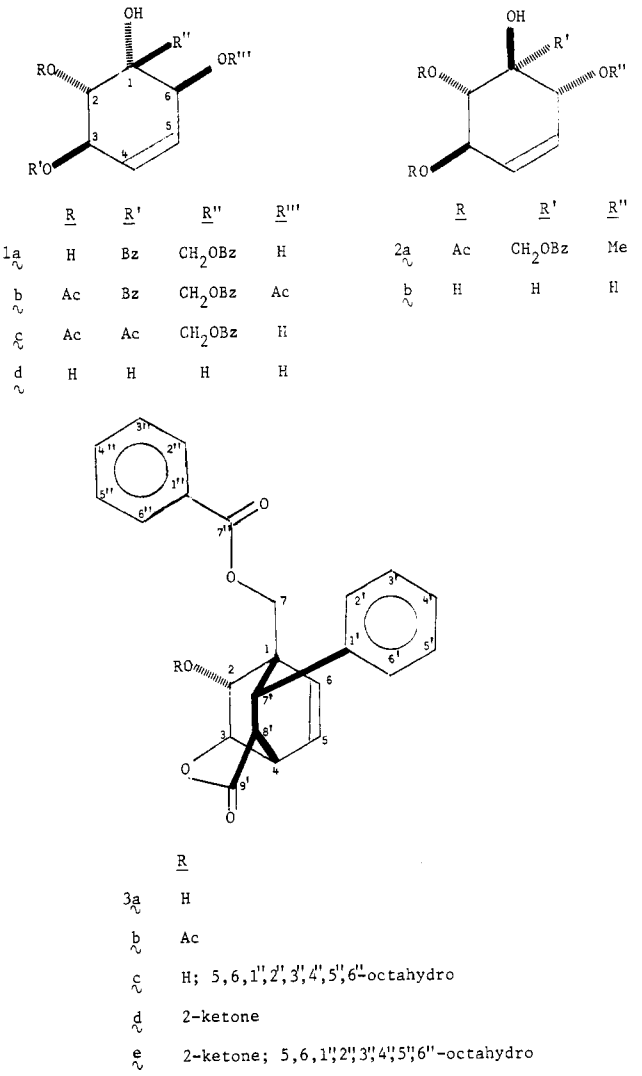
Zeylenol (**1a**, mp 144–145 °C) analyzed for $C_{21}H_{20}O_7$ (mol wt by EI and CI mass spectra 384). It exhibited λ_{max} 227 nm (ϵ 16457), the high intensity suggesting the presence of at least two chromophores. The IR spectrum indicated secondary and tertiary hydroxyl groups (3590, 3460, 1372, 1110, 1065 cm^{-1}), an alkene linkage (3080, 3020 cm^{-1}), an ester group (1720, 1270 cm^{-1}), and a monosubstituted phenyl ring (1601, 1582, 1490, 700 cm^{-1}).

The ^1H NMR spectral parameters of **1a** and related compounds are summarized in Table I. The spectra were analyzed with the aid of decoupling and computer simulation. The pattern of aromatic protons indicated two slightly different benzoyl groups, and the overall spectrum of **1a** was quite similar to that of seneol (**2a**), a constituent of the fruits of *Uvaria catocarpa*.[1] One benzoate grouping was clearly at C7 as in all compounds in this series, and the second had to be at C3 from the downfield position of HC3. Close examination of the coupling constants in **1a–d**,[2] **2a**, and **2b**[2] showed zeylenol to have the stereochemistry shown; particularly informative were the homoallylic couplings $^5J_{3,6}$, which were ~1 Hz in **1a,b** (typical for $^5J_{ae}$) and ~3 Hz in **2a** (characteristic for $^5J_{aa}$).[2] Also helpful was $^3J_{5,6}$, which in **1a** had an equatorial value of 4 Hz but in **2a** was only 1.9 Hz (axial).[2] In addition, $^3J_{2,3}$, which was 8.5 Hz in **2a** (axial–axial) with its one greatly favored half-chair conformation, was reduced to 7.4 Hz in **1b** (indicating the presence of about 15% of the other half-chair) and to 6.1 Hz in **1a** (showing about 35% of the other half-chair).[2]

The ^{13}C NMR chemical shifts and off-resonance multiplicities (given by a letter after the shift value) in Table II supported structure **1a** for zeylenol; corresponding data are not available for closely related compounds such as **1c** and **1d**.

The mass spectral fragmentation pattern (Scheme I) of zeylenol (**1a**) also supported the proposed structure. The elemental compositions of all peaks shown in Scheme I were verified by high-resolution exact-mass measurements, and where indicated, metastable peaks substantiated the proposed transformations. The M – $PhCO_2H$ species (*m/e* 262) broke down by a pattern similar to that observed for senepoxyde (**4**), another *Uvaria catocarpa* constituent,[1] suggesting that a large portion of the *m/e* 262 ion was a similar epoxide as shown. The mass spectral fragmentation pattern of zeylenyl diacetate (**1b**), which was very close

Chart I



	R	R'	R''	R'''
1a	H	Bz	CH_2OBz	H
b	Ac	Bz	CH_2OBz	Ac
c	Ac	Ac	CH_2OBz	H
d	H	H	H	H

	R	R'	R''
2a	Ac	CH_2OBz	Me
b	H	H	H

	R
3a	H
b	Ac
c	H; 5,6,1'',2'',3'',4'',5'',6''-octahydro
d	2-ketone
e	2-ketone; 5,6,1'',2'',3'',4'',5'',6''-octahydro

(1) Hollands, R.; Becher, D.; Gaudemer, A.; Polonsky, J.; Ricroch N. *Tetrahedron* **1968**, *24*, 1633.
(2) Abraham, R. J.; Gottschalck, H.; Paulsen, H.; Thomas, W. A. *J. Chem. Soc.* **1965**, 6268.

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Scheme I. Major Fragment Ions in the Mass Spectrum of Zeylenol (1a), with the Percent of Base Peak in Parentheses

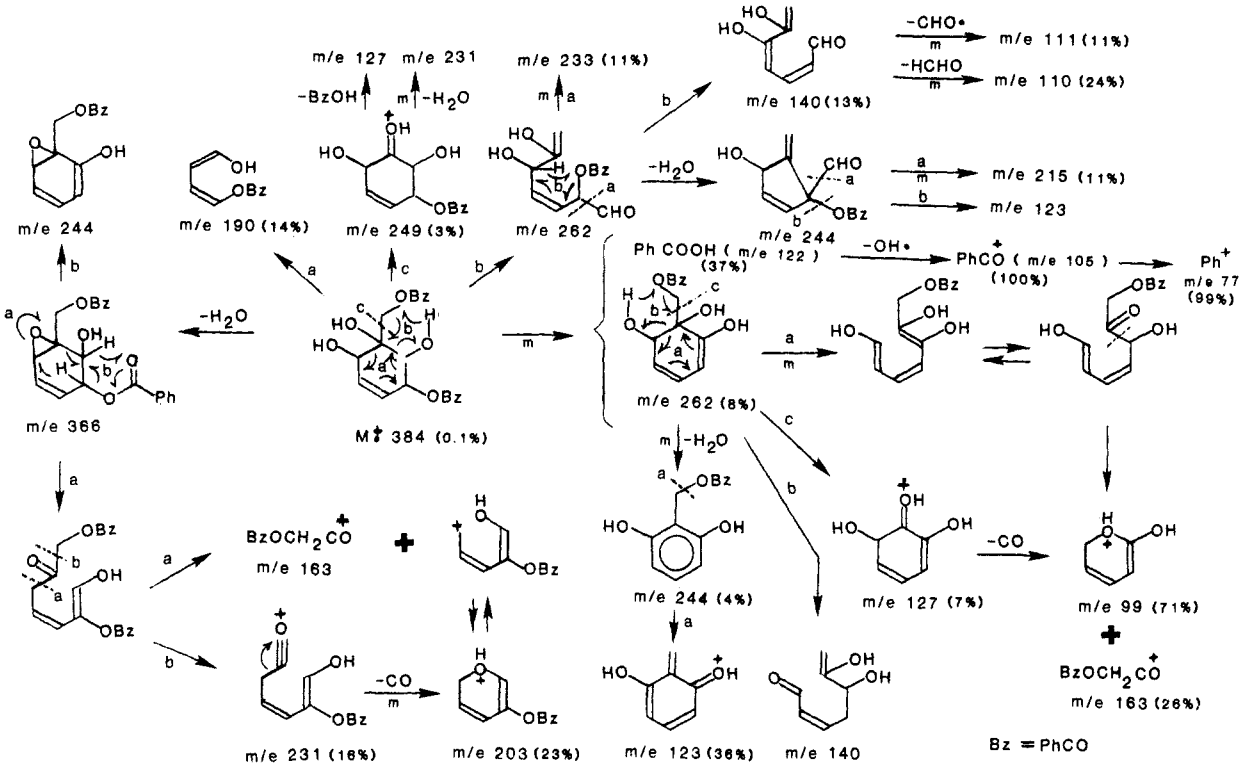


Table I. ^{1}H NMR Chemical Shifts ($CDCl_3$) of Zeylenol (1a) and Related Compounds

	chemical shift, δ						
atoms	1a	1b	1c[1]	1d[2]	2a	2a[a]	2b[2]
H2	4.22	5.72	5.50	3.83	5.30	5.584	3.44
H3	5.70	5.89	5.50	4.20	5.72	5.96	4.17
H4	5.88	6.01	5.80	5.79	5.85	5.433	5.61
H5	5.99	5.96	5.80	5.79	5.725	5.447	5.61
H6	4.32	5.52	4.45	3.83	4.10	3.705	3.44
H7	4.75 4.89	4.46 4.63	4.55		4.55 4.77	4.58 4.85	
H2′, H2″	7.97 8.02	7.98			8.09	8.15	
H3′, H3″	7.40	7.40			7.47	~7.06	
H4′, H4″	7.55	7.54			7.59	~7.06	
OH1	3.18	3.29			4.07	4.18	
OH2	2.96						
OH6	3.32						
OAc		2.09 2.11	1.97 2.1		1.75 2.03	1.45 1.64	
OMe					3.60	3.22	

atom	J, Hz						
no.	1a	1b	1c[1]	1d[2]	2a	2a[a]	2b[2]
2,3	6.1	7.4		4.4	8.5	8.5	8.3
2,7	0.0	0.0			0.9	0.9	
3,4	2.6	2.2		1.9	~1.9	~0.3	1.9
3,5	−1.6	−1.5		−2.1	~−2.2	~0.3	−2.1
3,6	1.1	0.8		1.0	~2.7	2.9	3.0
4,5	10.1	10.3			10.5	10.5	
4,6	−0.7	−0.3		−0.5	~0.0	~0.3	−2.1
5,6	4.0	4.0	3.5	5.3	~1.9	~0.3	1.9
7,7	−12.3	−11.8			−12.9	−12.9	

[a] In benzene-d_6.

to that of senepoxyde (4), conformed well to this scheme.

The absolute configuration shown for 1a and 1b is based on comparison with 1c;[1] all three compounds have large negative rotations.

Table II. ^{13}C NMR Chemical Shifts (δ, $CDCl_3$) of Zeylenol (1a) and Zeylena (3a)

atom	1a	3a
C1	76.0 s	51.2 s
C2	68.7 d	73.0 d
C3	74.4 d	83.3 d
C4	127.0 d	47.3 d
C5	129.5 d	127.7 d
C6	70.9 d	132.3 d
C7	66.8 t	62.3 t
C1′	128.5 s	139.2 s
C2′	129.9 d	128.4 d
C3′	128.5 d	129.5 d
C4′	133.5 d	127.5 d
C7′	165.0 s	45.9 s
C8′		40.2 d
C9′		178.0 s
C1″	128.5 s	128.4 s
C2″	129.9 d	129.9 d
C3″	128.5 d	128.8 d
C4″	133.5 d	133.9 d
C7″	165.0 s	167.3 s

Zeylena (3a) (mp 204–205 °C; $[\alpha]^{25}_D$ -136.3°) gave an elemental analysis corresponding to a molecular formula $C_{23}H_{20}O_5$, consistent with the molecular weight 376 provided by EI mass spectroscopy. The CI mass spectrum, however, displayed a peak at *m/e* 752, suggesting that zeylena either had molecular weight 752 or thermally formed a dimer in the ion source prior to ionization. The latter alternative was favored by gel-permeation chromatography and vapor-pressure osmometry, both of which indicated a molecular weight of about 380. The UV spectrum of zeylena (3a) provided the same absorption maximum (227 nm) and nearly the same intensity of absorption as zeylenol (1a). The IR spectrum ($CHCl_3$) showed bands for the presence of many of the structural elements of zeylenol (1a); the most striking difference was the appearance of a strong band at 1780 cm^{-1} in the new compound, indicating the presence of a saturated γ-lactone ring.

Table III. ^{1}H NMR Chemical Shifts ($CDCl_3$) of Zeylena (3a) and Zeylena Acetate (3b) with Crystallographically Determined Dihedral Angles (deg) in Parentheses after Vicinal Coupling Constants

	chemical shift, δ	
atoms	3a	3b
H2	3.85	5.17
H3	4.38	4.30
H4	3.67	3.65
H5	6.49	6.50
H6	5.83	5.93
H7	3.83	3.90
	4.88	4.53
H2′ to H6′	7.19	7.16
H7′	3.23	3.38
H8′	3.79	2.80
H2″, H6″	8.02	8.05
H3″ to H5″	7.55	7.55
OH	3.09	
OAc		1.99

	J, Hz	
atoms	3a	3b
2,3	0 (102)	0
2,OH	6.5 (53)	
3,4	5.0 (45)	5.0
3,8′	1.0	1.0
4,5	6.5 (2)	6.5
4,8′	4.5 (54)	4.5
5,6	8.0 (9)	8.0
7,7	11.5	11.5
7′,8′	2.0 (108)	2.0
ortho	8.0	8.0
meta	2.0	2.0

The ^{1}H NMR spectrum (Table III) of zeylena (**3a**), like that of zeylenol (**1a**), displayed signals for ten aromatic protons, but the splitting pattern indicated the presence of a monosubstituted phenyl (a 5 H multiplet centered at δ 7.2) and a benzoyl group (a 3 H multiplet centered at δ 7.6 and a 2 H doublet of doublets centered at δ 8.0). A 2 H AB quartet at δ 3.8 and 4.9 (J = 11.5 Hz) indicated that zeylena (**3a**) had also a (benzoyloxy)methylene group as in **1a**. Unlike **1a**, it had signals [δ 3.08 (d, 1 H, J = 6.5 Hz)] for only one secondary hydroxyl group, which was lost on deuteration as well as on acetylation (the acetate derivative, **3b**, showed the expected IR and ^{1}H NMR features and an appropriate shift of the molecular ion peak to m/e 418 in the mass spectrum). The remaining seven protons were all in methinyl groups (shown clearly by the ^{13}C NMR data in Table II), two of which were in a cis 1,2-disubstituted alkene (J = 8.0 Hz). The only biogenetically reasonable structure we could find which fit the data at this point was **3a**.

The mass spectrum of zeylena (**3a**) displayed fragment ions which are interpretable as shown in Scheme II. Other structures are possible for many of the fragments, but the molecular formulas of all fragments are correct (high-resolution mass spectroscopy), and in most cases, as indicated, the transitions shown are substantiated by metastable peaks. Benzoic acid is lost in at least two ways to give the m/e 254 peak, since no single structure can reasonably give all of the further cleavages observed. High-resolution showed the m/e 210 peak (64% of base peak) to consist of $C_{14}H_{10}O_2$ and $C_{15}H_{14}O$ in a 3:1 ratio as shown in Scheme II. The base peak at m/e 105 is due to $PhCO^+$. The peak at m/e 752 in the CI mass spectrum probably comes from retro-Diels–Alder reaction followed by intermolecular Diels–Alder reaction during heating for volatilization.

Structure **3a** for zeylena was conclusively established (except for the absolute configuration) by an X-ray study.

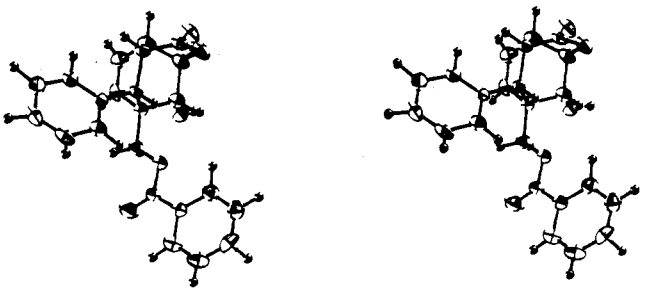


Figure 1. Stereoscopic view of zeylena (**3a**). Hydrogen atoms are shown as spheres and other atoms as 50% probability ellipsoids.

Figure 1 depicts the molecule. The hydrogen positions were successfully refined, with the final R being 0.037. Hydrogen bonding occurs intermolecularly from the OH to the lactone C=O of the corresponding molecule in the next cell in the a direction. Dihedral angles pertinent for correlation with vicinal H–H coupling constants in the ^{1}H NMR spectrum of zeylena (**3a**) are shown in parentheses in Table III.

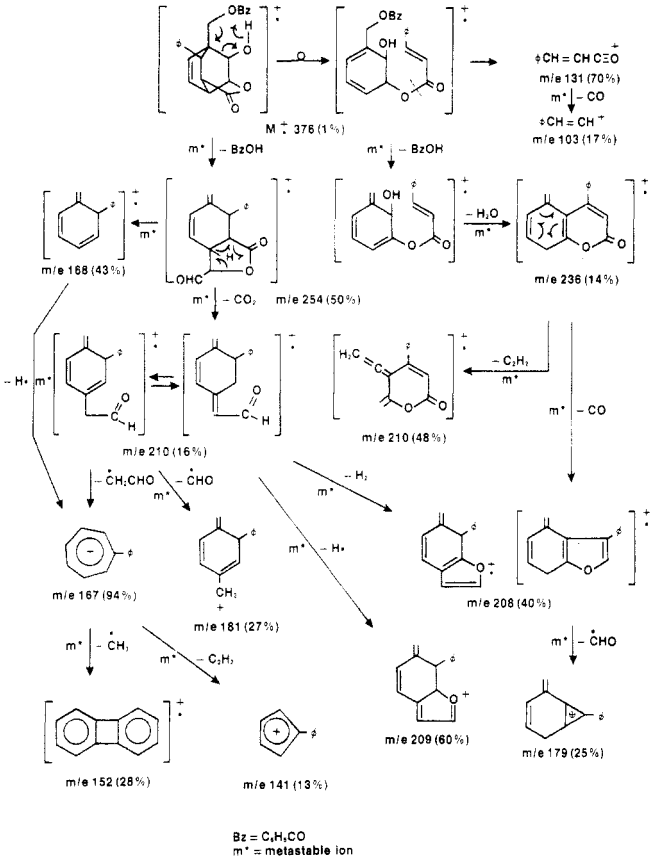
Acetylation of **3a** with acetic anhydride–pyridine gave a monoacetate (**3b**, mp 148 °C), which was confirmed by its IR (no hydroxyl band, new ester band at 1745 cm^{-1}), ^{1}H NMR (Table III), and (mass M^+·, m/e 418) spectra. The absence of hydroxyl in **3b** directed the elimination of benzoic acid toward the reverse Diels–Alder path in Scheme II as expected. The CI mass spectrum of **3b** displayed a molecular ion peak at m/e 836, indicating dimerization.

Catalytic (PtO_2) hydrogenation of zeylena (**3a**) in MeOH–AcOH at atmospheric pressure yielded a mixture of two compounds (TLC). The lower R_f material (major product) was 5,6,1″,2″,3″,4″,5″,6″-octahydrozeylena (**3c**): mp 168–169 °C; UV, rising end absorption; IR, weak phenyl bands; ^{1}H NMR, only five aromatic protons. The EI mass spectrum of **3c**, which exhibited a molecular ion peak at m/e 384 (m/e 768 by CI mass spectroscopy), showed that the phenyl ring of the CH_2OBz group and the double bond had been reduced. Peaks associated with M - $C_6H_{11}COOH$ (43%), $[C_6H_{11}COOH]^+$· (18%), $C_6H_{11}C{\equiv}O^+$ (33%), $C_6H_{11}^+$ (base peak), and $C_4H_7^+$ (64%) clearly provided evidence for the formation of **3c**. No further attempt was made to characterize the upper R_f material (minor product) in which both the phenyl rings and the double bond appear to be reduced as judged from its IR spectrum which showed no unsaturation or phenyl bands.

Jones oxidation of zeylena (**3a**) also yielded a mixture of two compounds (TLC). The upper R_f material, dehydrozeylena (**3d**; mp 119–121 °C; new carbonyl band at 1726 cm^{-1} in the IR spectrum), did not give a dimer peak in the CI mass spectrum presumably because its retro-Diels–Alder reaction is rapidly followed by tautomerization to a phenol. An attempt to determine the absolute configuration of these substances from its CD curve at 290 nm was not definitive, due to strong absorption by the benzoyl group in this region. Oxidation of the octahydro derivative **3c**, however, gave ketone **3e** with a positive CD curve at 308 nm, favoring the absolute configurations depicted for these substances.

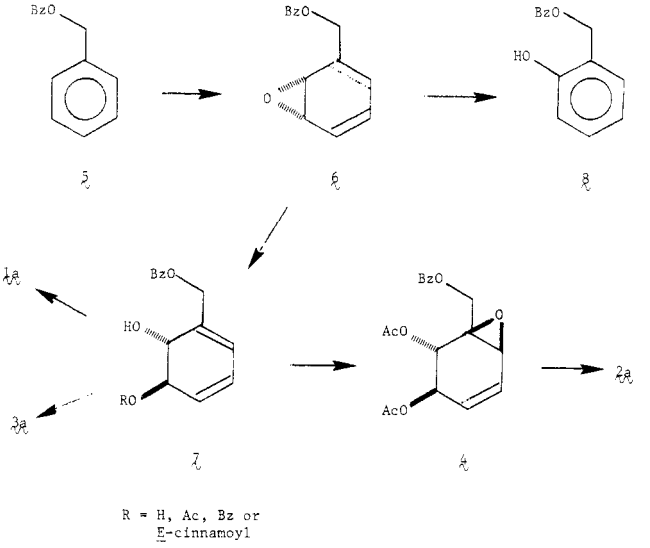
The finding of zeylenol (**1a**) and zeylena (**3a**) in a *Uvaria* species makes clearer the biogenetic routes to some related substances found in this genus as shown in Scheme III. Benzyl benzoate (**5**) is epoxidized to key intermediate **6**.[3]

Scheme II. Major Fragment Ions in the Mass Spectrum of Zeylena (3a), with the Percent of Base Peak in Parentheses



Compound **6** adds (*E*)-cinnamic acid to give **7** (R = (*E*)-cinnamoyl), which undergoes an intramolecular Diels–Alder reaction to give zeylena (**3a**).[4] Compound **6** also adds water, acetic acid, or benzoic acid and becomes further epoxidized, eventually giving three other natural products: zeylenol (**1a**), senepoxyde[1] (**4**), and seneol[1] (**2a**).[5] Via **8**, **6** is also the source of the *o*-hydroxybenzyl groups found in uvarinol[6] (which contains three such groups and one cinnamic acid derived group), chamanetin,[7] isochamanetin,[7] and uvaretin[8] (all three of which contain one *o*-hydroxybenzyl group and one cinnamic acid derived group);[3] dilute acid should rearrange **6** into **8** since the intermediate cyclohexadienyl cation leading to **8** is more stable than the alternative one.

Scheme III. Biosynthesis of *Uvaria* Compounds from Benzyl Benzoate (5)

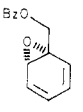


Experimental Section

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Carbon and hydrogen analyses were carried out by the University Analytical Center, Tucson, AZ. Optical rotations were measured by using a Perkin-Elmer 241 MC polarimeter. Ultraviolet (UV) and infrared (IR) spectra were run on Cary 15 and Beckman IR-33 spectrometers, respectively. ^{1}H NMR spectra were run at 250 MHz on a Bruker WM250 spectrometer, and ^{13}C NMR spectra were run at 22.63 MHz on a Bruker WH-90 spectrometer; in both cases the shifts are given as parts per million downfield from Me_4Si (δ). Electron impact (EI) and chemical ionization (CI) mass spectra were recorded on a Varian MAT 311A spectrometer with a Varian SS 200 data system, and the intensities of the ions, given in parentheses, are expressed on a scale in which the largest peak in the spectrum is assigned an intensity of 100%. The high-resolution data were obtained at a resolution of 7000 by scanning the mass range from m/e 100 to 500 repetitively at 25 s/decay with PFK as the internal standard. Metastable ion spectra were recorded by either scanning the magnetic (B) and electrostatic (E) fields at a constant accelerating voltage with the B/E ratio constant to obtain the daughters of parents or by scanning the accelerating voltage at constant B and E for determination of parents of daughters. Samples were introduced by using a direct probe. The normal ionizing voltage was 70 eV with a source temperature of 250 °C. Gel-permeation chromatography (GPC) was carried out in THF by using a Varian 5000 high-pressure liquid chromatograph equipped with an RI detector and a Micropak TSK Gel 2000 H column.

Isolation of Zeylenol (1a) and Zeylena (3a). The dried roots of *Uvaria zeylanica*, collected in Sri Lanka in April of 1978, were ground in a Wiley mill and stored at -10 °C prior to extraction. The ground material (5.5 kg) was extracted with methanol by being stirred mechanically at room temperature for 24 h and filtered, and the filtrate was air-dried. The resulting methanol-soluble residue (835 g) was repeatedly triturated with acetone and then stirred magnetically for 6 h. The mixture was allowed

(3) Compound **6** has been proposed (Ganem, B.; Holbert, G. W. *Bioorg. Chem.* **1977**, *6*, 393. Ganem, B.; Holbert, G. W.; Weiss, L. B.; Ishizumi, K. *J. Am. Chem. Soc.* **1978**, *100*, 6483) as a precursor of **4** via a diepoxide intermediate. **3a** clearly does not come from a diepoxide but rather from an intermediate of type **7**; this suggests that **1a**, **2a**, and **4** may also arise via intermediates of type **7** rather than via a diepoxide. Another alternative biogenetic route involves benzene oxide i as an intermediate rather than **6**, with *conjugate* addition to give **7** (we thank Dr. Barry M. Trost for mentioning this possibility). Since it is not possible for i to yield **1a** and **2a** without a *simple* addition to a conjugated epoxide, we favor **6** over i as shown in Scheme III.



i

(4) For other examples of possible biosynthetic Diels–Alder reactions, see: Bazan, A. C.; Edwards, J. M.; Weiss, U. *Tetrahedron* **1978**, *34*, 3005. Stipanovic, R. D.; Bell, A. A.; O'Brien, D. H.; Lukefahr, M. J. *Tetrahedron Lett.* **1977**, 567. Dominguez, X. A.; Martinez, C.; Calero, A.; Dominguez, X. A., Jr.; Hinojosa, M.; Zamudio, A.; Zabel, V.; Smith, W. B.; Watson, W. H. *Tetrahedron Lett.* **1978**, 429. Westley, J. W.; Evans, R. H., Jr.; Liu, C. M.; Hermann, T.; Blount, J. F. *J. Am. Chem. Soc.* **1978**, *100*, 6784.

(5) It has been shown[1] that senepoxyde (**4**) ring opens to products of type **1** and **2**, obviating the need for an epoxide intermediate with any other stereochemistry.

(6) Hufford, C. D.; Lasswell, W. L.; Hirotsu, K.; Clardy, J. *J. Org. Chem.* **1979**, *44*, 4709.

(7) Hufford, C. D.; Lasswell, W. L. *J. Org. Chem.* **1976**, *41*, 4052.

(8) Cole, J. R.; Torrance, S. J.; Wiedhopf, R. M.; Arora, S. K.; Bates, R. B. *J. Org. Chem.* **1976**, *41*, 1852.

to stand overnight at room temperature and was filtered, and the filtrate was air-dried. The acetone-soluble residue (508 g) was repeatedly triturated with ether followed by magnetic stirring for about 6 h and filteration, and the filtrate was concentrated to about 500 mL in vacuo. After the mixture was allowed to stand in the refrigerator for 2 days, a heavy deposit of crude crystals of zeylena (**3a**) formed which were separated by filtration, washed with cold ether, and dried (8 g).

The resulting mother liquor, obtained after separation of zeylena (**3a**) from the ether-soluble concentrate, was evaporated in vacuo, and the residue (110 g) was subjected to three-funnel partitioning between cyclohexane (1750 mL), methanol (1250 mL), and water (250 mL). The residue (42 g) obtained from the lower phase (air-dried) was stirred with ether for about 3 h, left in the refrigerator overnight, and filtered, and the filtrate was evaporated to dryness in vacuo. Chromatography of this ether-soluble residue (40 g) on EM silica gel 60 (800 g) and elution with ether gave a fraction which on concentration and cooling deposited additional crystals of crude zeylena (**3a**, 0.6 g) which were separated by filtration. The mother liquor was evaporated to dryness in vacuo, and the residue (27 g) was subjected to EM silica gel 60 (540 g) column chromatography. The column was eluted with *n*-hexane followed by *n*-hexane containing gradually increasing amounts of ethyl acetate, and several 500-mL fractions were collected. Fractions 30–31, which displayed essentially one major spot on TLC, yielded crude zeylenol (**1a**, 0.9 g).

Zeylenol (1a). This substance was crystallized from ethyl acetate as colorless needles: mp 144–145 °C; $[\alpha]^{25}_D$ -116.3° (*c* 0.915, $CHCl_3$); UV (MeOH) λ_{max} 227 nm (ϵ 16 457); IR ($CHCl_3$) 3590, 3460, 3080, 3020, 1720 (br), 1601, 1582, 1490, 1450, 1372, 1313, 1270, 1110, 1090, 1065, 1038, 700 cm^{-1}; mass spectrum, *m/e* (relative intensity) 384 ($M^{+}\cdot$), 262 (8), 249 (3), 244 (4), 233 (11), 231 (16), 215 (11), 203 (23), 190 (14), 163 (26), 123 (36), 122 (39), 105 (100), 99 (71), 77 (99), 51 (30). The spectra were in accord with structure **1a**.

Anal. Calcd for $C_{21}H_{20}O_7$: C, 65.52; H, 5.24. Found: C, 65.37; H, 5.23.

Zeylenyl Diacetate (1b). Acetylation of zeylenol (**1a**) in pyridine–acetic anhydride at room temperature overnight yielded **1b** which remained foamy but was homogeneous on TLC: $[\alpha]^{25}_D$ -23° (*c* 1, $CHCl_3$); IR (CCl_4) 3460, 3070, 3040, 1760, 1730, 1645, 1600, 1585, 1490, 1450, 1370, 1313, 1265, 1220, 1175, 1108, 1020, 970, 910, 700 cm^{-1}; mass spectrum, *m/e* (relative intensity) 408 (3), 346 (2), 286 (3), 273 (14), 244 (10), 231 (5), 226 (10), 183 (14), 163 (48), 141 (32), 122 (32), 105 (100), 99 (18), 77 (56). The spectra were in accord with structure **1b**.

Zeylena (3a). This substance was crystallized from 50% methanolic methylene chloride: mp 204–205 °C; $[\alpha]^{25}_D$ -136.3° (*c* 1.772, $CHCl_3$); UV (MeOH) λ_{max} 227 nm (ϵ 13 330); IR (KBr) 3420, 3090, 3060, 3040, 3000, 1750, 1710, 1600, 1580, 1490, 1450, 1400, 1350, 1310, 1275, 1170, 1110, 1060, 980, 950, 920, 765 700 cm^{-1}; mass spectrum, *m/e* (relative intensity) 376 ($M^{+}\cdot$), 254 (50), 236 (14), 228 (5), 226 (10), 210 (64), 209 (60), 208 (40), 195 (23), 192 (19), 191 (14), 181 (27), 179 (24), 168 (43), 167 (94), 165 (41), 154 (10), 153 (16), 152 (28), 141 (13), 131 (70), 128 (14), 122 (6), 115 (18), 106 (55), 105 (100). The spectra were in accord with structure **3a**.

Anal. Calcd. for $C_{23}H_{20}O_5$: C, 73.40; H, 5.32. Found: C, 73.40; H, 5.30.

Zeylena Acetate (3b). This substance, prepared as above, crystallized from CH_2Cl_2/MeOH as colorless flakes: mp 148 °C; UV (MeOH) λ_{max} 227 nm (ϵ 11 277); IR ($CHCl_3$) 1775, 1745, 1715, 1270, 1255 cm^{-1}; mass spectrum, *m/e* (relative intensity) 418 ($M^{+}\cdot$), 376 (2), 358 (1), 296 (4), 275 (4) 254 (13), 236 (3), 228 (21), 210 (7), 209 (9), 208 (5), 192 (11), 181 (4), 179 (4), 167 (21), 131 (100), 106 (26) 105 (100), 91 (11), 77 (49). The spectra were in accord with structure **3b**.

Anal. Calcd for $C_{25}H_{22}O_6$: C, 71.77; H, 5.26. Found: C, 71.7; H, 5.3.

5,6,1″,2″,3″,4″,5″,6″-Octahydrozeylena (3c). A solution of zeylena (**3a**, 250 mg) in glacial AcOH (10 mL) and MeOH (25 mL) was hydrogenated at room temperature by using PtO_2 (220 mg). The reaction was stopped after 1 h, the mixture filtered, and the solvent removed in vacuo. TLC revealed that the residue was a mixture of two components in the ratio of approximately 8:2. The lower R_f material (major component) was separated by preparative TLC (EM silica gel 60 PF-254; hexane–EtOAc, 6:4) and crystallized from ether as colorless prisms: mp 168–169 °C; UV (MeOH) end absorption; IR ($CHCl_3$) 3500, 3010, 1780, 1718, 1605 (w), 1585 (w), 1500 (w) cm^{-1}; ^1H NMR ($CDCl_3$) 3.62 (brs, 1 H, H2), 4.46 (brd, 1 H, H3), 4.18 and 3.08 (AB q, 2 H, J_{gem} = 11.5 Hz, H7), 3.26 (brs, 1 H, OH), 3.00 (brs, 1 H, H7′), 2.80 (m, 1 H, H8′), 2.75 (m, 1 H, H4), 7.30 (brs, 5 H, H2′–H6′); mass spectrum, *m/e* (relative intensity) 384 ($M^{+}\cdot$), 366 (32), 294 (15), 256 (43), 238 (10), 228 (17), 212 (13), 211 (11), 210 (32), 199 (23), 194 (16), 187 (28), 184 (24), 183 (12), 182 (2‖, 181 (31), 170 (15), 169 (78), 168 (29), 167 (23), 166 (17), 154 (6), 142 (13), 141 (20), 129 (28), 128 (18), 115 (21), 111 (33), 91 (64), 83 (100), 55 (77). The spectra were in accord with structure **3c**.

Anal. Calcd for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34. Found: C, 72.00; H, 7.35.

Dehydrozeylena (3d). To a cold solution of zeylena (**3a**, 0.2 g) in acetone (20 mL) was added Jones reagent dropwise with stirring until the orange color persisted. After the usual workup, the reaction product, which showed two components on TLC, was subjected to preparative TLC (hexane–EtOAc, 70:30). The upper R_f material was crystallized from ether: mp 119–121 °C; UV (MeOH) λ_{max} 226 nm (ϵ 14 442); IR ($CHCl_3$) 1792, 1748, 1726 cm^{-1}; mass spectrum, *m/e* (relative intensity) 374 ($M^{+}\cdot$, 10), 346 (1), 273 (12), 255 (2), 252, (3), 224 (8), 196 (10), 195 (7), 179 (6), 168 (60), 167 (47), 152 (10), 131 (82), 122 (4), 105 (100), 91 (10), 77 (64), 51 (18). The spectra were in accord with structure **3d**.

Anal. Calcd for $C_{23}H_{18}O_5$: C, 73.7; H, 4.84. Found: C, 73.2; H, 5.0.

Dehydro-5,6,1″,2″,3″,4″,5″,6″-Octahydrozeylena (3e). Chromic anhydride (0.3 g) was dissolved in a cold solution of pyridine (5 mL) and methylene chloride (5 mL). To this solution was added Celite (1 g) followed by a cold solution of 5,6,1″,2″,3″,4″,5″,6″-octahydrozeylena (**3c**, 0.15 g) in methylene chloride (5 mL), and the mixture was left overnight. After the workup, an analytical sample of **3e**, which remained foamy, was isolated by preparative TLC. The IR [($CHCl_3$) 1792, 1745, 1725 cm^{-1}] and mass [*m/e* (relative intensity) 382 ($M^{+}\cdot$, 6), 354 (2), 254 (10), 226 (15) 198 (34), 197 (9), 169 (24), 141 (6), 129 (9), 128 (8), 111 (63), 91 (19), 83 (100), 55 (30)] spectra were in accord with structure **3e**.

Crystallographic Study of Zeylena (3a). A 0.2 × 0.5 × 0.8 mm crystal grown from 1:1 methanol–methylene chloride was mounted on a Syntex $P2_1$ diffractometer with a graphite monochromator (Mo Kα, λ 0.710 69 Å). The cell lengths, determined by least-squares treatment of 13 reflections, were a = 7.235 (2), b = 14.004 (6), c = 18.123 (4) Å; the space group was $P2_12_12_1$ with Z = 4. The θ–2θ scan technique was used at a variable scan rate of 2.0–29.3°/min with a 2° scan range and background to scan time ratio 1.0. A total of 1976 reflections with $2\theta < 50°$ were measured and 1914 with intensities $>3\sigma(I)$ were considered observed. There were no significant variations in the intensities of check reflections. Standard deviations were assigned as described by Corfield et al.,[9] the value of p being 0.04.

E maps based on MULTAN[10] solutions using the top 300 E's were unhelpful, but when the top 200 E's were used, all nonhydrogen atoms were located on the first E map. Full-matrix least-squares refinement using isotropic temperature factors reduced R to 0.10; with anisotropic factors, R dropped to 0.07. Hydrogen positions were calculated, and when hydrogens were included in further refinements with the isotropic temperature factors of the atoms to which they were attached, R dropped to its final value of 0.037. The scattering factors used were those of Hanson et al.[11] No correction was applied for extinction.

Acknowledgment. This investigation was supported by Grants No. 5-R01-CA22336-02 and 1-R01-CA29626-01,

(9) Corfield, P. W. R.; Doedens, R. J.; Ibers, J. A. *Inorg. Chem.* **1967**, *6*, 197.

(10) Germain, G.; Main, P.; Woolfson, M. M. *Acta Crystallogr., Sect. B* **1970**, *B26*, 274.

(11) Hanson, H. P.; Herman, F.; Lea, J. D.; Skillman, S. *Acta Crystallogr., Sect. B* **1964**, *B17*, 1040.

(12) Note Added in Proof: From the same plant, we have just isolated what is apparently the C1 epimer of zeylenol (**1a**), and are undertaking an X-ray study on it to test the possibility that we have the C1 configurations of these two substances reversed.

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Registry No. **1a**, 78804-17-8; **1b**, 78804-18-9; **3a**, 78804-19-0; **3b**, 78804-20-3; **3c**, 78804-21-4; **3d**, 78804-22-5; **3e**, 78804-23-6.

Supplementary Material Available: Tables IV–VIII containing exact mass measurements, fractional coordinates, temperature factors, bond distances, and bond angles and Figure 2, a packing diagram (7 pages). Ordering information is given on any current masthead page.

Total Synthesis of (±)-Multifidene, the Gamete Attractant of the Phaeophyte *Cutleria multifida*

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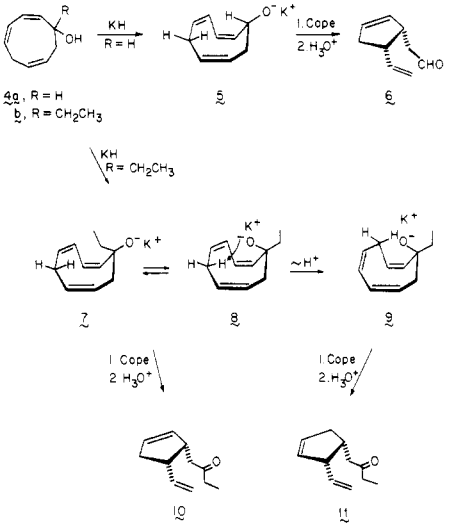
A short, stereoselective total synthesis of racemic multifidene has been achieved. The key elements of the synthetic scheme are (i) oxyanionic Cope rearrangement of *cis*[3]-2,4,7-cyclononatrienol and in situ trapping of the resulting enolate with chlorotrimethylsilane, (ii) stereocontrolled introduction of a phenylseleno group α to the aldehyde functionality, (iii) addition of an ethyl fragment under conditions where the polar PhSe substituent can induce high levels of stereoselection, and (iv) a double inversion sequence to introduce a cis double bond cleanly.

The anisogamous marine brown alga *Cutleria multifida* (Smith) Grev., which can be found in the springtime at various locales along the Mediterranean coast, achieves reproduction by sexual chemotaxis.[1] The vital need for successful fertilization begins when a larger female gynogamete of the Phyophyte releases a small quantity[2] of a volatile three-component hydrocarbon mixture in order to attract to itself tiny androgametes (sperm). After these have accumulated (sometimes violently and always in large numbers), mating occurs between a single pair and the resulting cell fusion leads to zygote formation. At this point, the supernumerary male cells lose interest and depart.[2-4] This dramatic long-range attraction of the sperm through the water has been shown to be triggered by multifidene (**1**), the male-attracting agent and major constituent of the hydrocarbon essential oil.[5,6] Subsequent synthetic studies by Jaenicke and Boland have led to the development of two viable routes to this biologically active substance.[7] Heating must be avoided during the final step which liberates **1** to avert contamination with the isomeric inactive hydrocarbons **2** and **3** to which multifidene is related by Cope rearrangement. We now describe a most direct and highly stereoselective total synthesis of multifidene (**1**) which takes advantage of the stereocontrolled anionic oxy-Cope ring contraction of *cis*[3]-2,4,7-cyclononatrienol[8] as well as the steric and chemical properties of a phenylselenyl substituent.

Scheme I



Our strategy centered around medium-ring alcohol **4a**, which was previously shown to undergo rapid isomerization at room temperature when in the form of its potassium alkoxide.[8] Mechanistically implicated in the efficient conversion to aldehyde **6** is the tublike conformer **5** wherein the alkoxide substitutent is oriented exo on the alicyclic framework, (Scheme I). When the ethyl homologue **4b** was similarly treated with potassium hydride in dry tetrahydrofuran, conversion to a mixture of the isom-

(1) Jaenicke, L.; Müller, D. G. *Fortschr. Chem. Org. Naturst.* **1973**, *30*, 61.

(2) A half-year of mass culture of the algae and extraction of the female gametes served to yield only 3.7 mg of the mixture: Müller, D. G. In "Marine Natural Products Chemistry"; Faulkner, D. J., Fenical, D. J., Eds.; Plenum Press: New York, 1977; pp 351–360.

(3) Müller, D. J. *Z. Pflanzenphysiol.* **1976**, *80*, 120.

(4) Jaenicke, L. In "Biochemistry of Sensory Functions"; Jaenicke, L., Ed.; Springer-Verlag: New York, 1974; pp 307–309.

(5) Jaenicke, L.; Muller, D. G.; Moore, R. E. *J. Am. Chem. Soc.* **1974**, *96*, 3324.

(6) Jaenicke, L.; Boland, W. *Justus Liebigs Ann. Chem.* **1976**, 1135.

(7) Boland, W.; Jaenicke, L. *Chem. Ber.* **1978**, *111*, 3262. These authors have also give attention to the synthesis of closely related molecules: *J. Org. Chem.* **1979**, *44*, 4819.

(8) (a) Paquette, L. A.; Crouse, G. D.; Sharma, A. K. *J. Am. Chem. Soc.* **1980**, *102*, 3972, (a) Paquette, L. A.; Crouse, G. D. *Tetrahedron*, in press.

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