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WIDESPREAD OCCURRENCE OF TWO HETEROANNULAR DIENES OF THE CADALANE SKELETON

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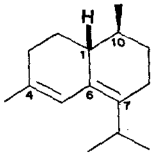
Key Word Index—Sesquiterpenes; zonarene; amorphanes; transoid butadiene chirality.

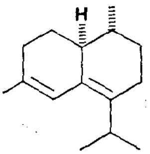
Abstract—Zonarene (II) and its epimer (I) have been identified as constituents in nine essential oils. Their structures and absolute configurations are established through chemical interrelationship with amorphenes and circular dichroism studies. Diene I occurs in both enantiomeric forms in nature.

INTRODUCTION

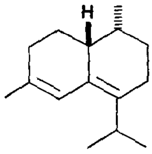
OVER the past few years, the analysis of sesquiterpene essential oils has been one of the areas of concern in our two laboratories. Two new heteroannular dienes (I, in both optical forms, and II) of the cadalane skeleton were encountered in a variety of oils and as rearrangement products of other cadalane dienes. Their structures were elucidated independently but by related routes.



((–)-I)
10-epizonarene
(–)-10 αH-muurola-4,6-diene



((+)-I)
ent-10-epizonarene



((–)-II)
zonarene
(–)-10β H-muurola-4,6-diene

The recent report of the isolation of these two substances (without specification of relative stereochemistry) from farnesol after chemical cyclization[1] and the report of zonarene (=(–)—II) from examination of the reported spectral data) isolated from the brown seaweed *Dictyopteris zonariodes*,[2] prompt us to report our work on these substances.

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* National Science Foundation Fellow, 1968–1971.

[1] OHTA, Y. and HIROSE, Y. (1972) *Chem. Letters Japan* 263.

[2] FENICAL, W., SIMS, J. J., WING, R. M. and RADLICK, P. C. (1972) *Phytochem.* **11**, 1161.

RESULTS AND DISCUSSION

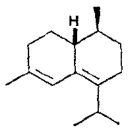
In Canada, (+)—I and (−)—II were first isolated from a sample of *Alpinia officinarium* oil. In Washington State, (−)—I and (−)—II were found in Alaska cedar (*Chamaecyparis nootkatensis*) and Cade oil (*Juniperus oxycedrus*), respectively. Subsequent to this both diastereomers have been found in *Zingiber officinale*, and isomer II in *Pelargonium graveolens*, *Pimenta diocia*, *Eugenia caryophyllus* and *Laurus noblis*. In addition, both isomers are encountered as products on acid treatment of various cadinene isomers. A comparison of the spectral data for samples of the two substances appears in Table 1. The IR spectra are reproduced in Fig. 1.

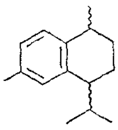
TABLE 1. SPECTRAL DATA FOR DIENES I AND II

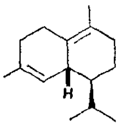
	Source	NMR (δ in ppm) doublet-CH_3; =C–H, =C–CH_3	UV $\epsilon_{245-248}$	CD $\Delta\epsilon$	$[\alpha]_D$
(−)—I	*Chamaecyparis nootkatensis*	3 *ca.* 0·99; 6·19, 1·77	16400	−15	−175
(+)—I	*Alpinia officinarum*	0·97, 0·98,† 1·00; 6·22, 1·75*	12000	+6·5	+ve
(+)—I	(+)-δ-Cadinene, HCO_2H	3 *ca.* 0·99; 6·20, 1·76	17800	+2·5	+95
(±)—I	Farnesol, BF_3[1]	3 *ca.* 0·94; 6·10, 1·71‡	18800	—	—
(−)—II	Cade oil	0·79, 2 *ca.* 0·96; 6·20, 1·74	10800	−6·6	−140
(−)—II	*Alpinia officinarum*	0·81, 0·95, 0·96;§ 6·27, 1·76*	13000	−4·8	−ve
(−)—II	Zonarene[2]	0·80, 2 *ca.* 0·95; 6·30, 1·75	19070	−ve	−218
(±)—II	Farnesol, BF_3[1]	0·78, 2 *ca.* 0·94; 6·10, 1·72‡	19600	—	—

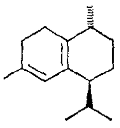
* Data obtained from 220 M Hz spectrum.
† The -$CHMe_2$ group appears as two 7 Hz doublets, $\Delta\delta = 0{\cdot}005$ ppm.
‡ Data suggests a calibration error.
§ The -$CHMe_2$ group appears as two 7 Hz doublets, $\Delta\delta = 0{\cdot}009$ ppm.

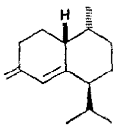
The isolation of these substances in pure form from most essentials oils requires extensive use of $AgNO_3$–Al_2O_3 chromatography prior to preparative GLC. For example, I elutes with β-alaskene on all gas chromatographic phases and II is similarly unresolved from δ-cadinene, a common congener (see Experimental).

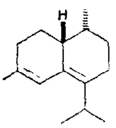

((−)-I)


(III)


(IV)


(V)


(VI)


((−)-II)

Structure Elucidation—Relative Stereochemistry

The cadalane skeleton was established by dehydrogenation (S, triglyme at reflux)[3] giving 90^+ % cadalene from either diastereomer. Partial aromatization with trifluoroacetic acid[4] afforded diastereomeric calamenenes (III) from dienes I and II in high yield. In the

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[3] ANDERSEN, N. H., FALCONE, M. S. and SYRDAL, D. D. (1970) *Phytochem.* **9**, 1341.
[4] ANDERSEN, N. H., SYRDAL, D. D. and GRAHAM, C. (1972) *Tetrahedron Letters* 903.

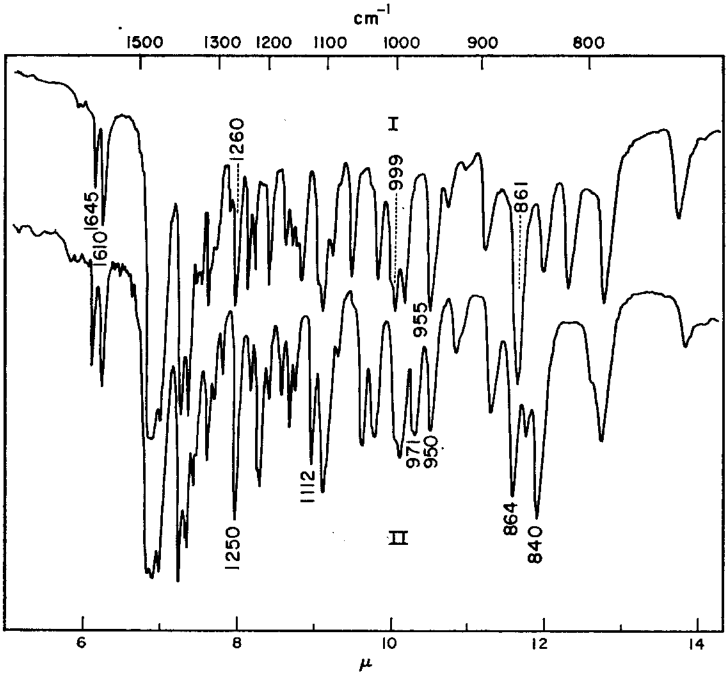


FIG. 1. IR SPECTRA OF ZONARENE (II) AND ITS EPIMER (I).

case of (—)—I, the product was 59% *cis* and showed a positive ^1L_b band[5] ($\Delta\epsilon_{278} = +0{\cdot}112$).* The cadalene skeleton was also suggested by the observation that dienes I and II result from isomerizations of known cadinenes:

$$\text{(IV)} \xrightarrow[\substack{100^\circ \\ 5\ \text{hr}}]{\text{HCO}_2\text{H}} (+)\text{—I (45\% yield, 17\% optical purity)}$$

$$\text{(VI)} \xrightarrow[\substack{80\%\ \text{aq. dioxane} \\ 50^\circ,\ 1\ \text{hr}}]{0{\cdot}012\ \text{N HCl}} \text{(V) (80\%) + (II) (10\%) + (III) (5\%)}$$

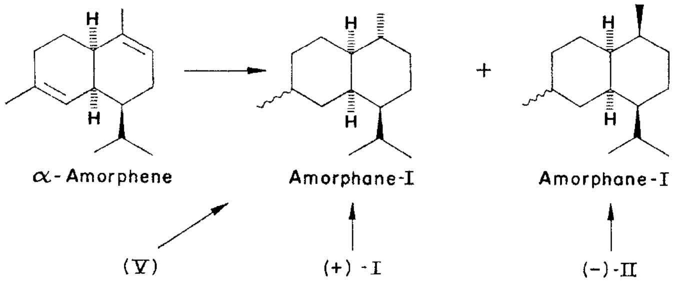
$$\text{(V)} \xrightarrow[80^\circ,\ 2\ \text{hr}]{0{\cdot}012\ \text{N HCl}} \text{(II) (8\%) + (I) (59\%) + (III) (13\%).}$$

The production of diene II (to the exclusion of I) under mild treatment of diene VI is in accord with the assigned relative stereochemistry.

* This observation is still somewhat confusing, since both diastereomers of III with retained stereochemistry at C-10 show negative ^1L_b bands.[5]

[5] ANDERSEN, N. H., SYRDAL, D. D. and GRAHAM, C. (1972) *Tetrahedron Letters* 905

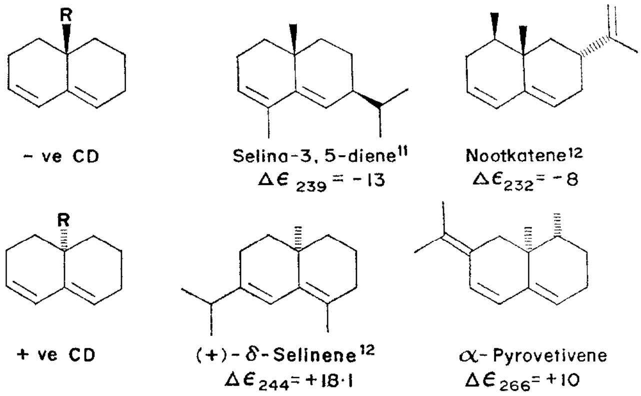
With the skeleton established, the NMR data define the position of the double bonds; in particular, the downfield vinyl hydrogen singlet must be internal in a butadiene with a substantial *peri* effect. The *cis*-1,10-hydrogen structure was assigned to isomer II based on the upfield position of the doublet methyl, reflecting the axial disposition of the group and its placement over the π-orbitals of the diene. This assignment was confirmed by the hydrogenation product correlations shown below:



It was found that α-amorphene[6] (or zizanene, its enantiomer[7]), diene V, and diene I had one product in common, amorphane-I.[8,9] Conversely, diene II had no products in common with diene V but did produce amorphane-II.[8,9] This establishes the relative stereochemistry at C-1 and C-10 in the isomers. Figure 2 gives the IR spectra of these two amorphanes.

Absolute Stereochemistry

The observed cotton effects of the butadiene chromophores was the basis for the assignment of the absolute configuration of the fusion hydrogen. The correlation follows from the examples below and is in accord with the transoid diene chirality rule.[10]



In the case of diene I, the assignment has been confirmed by ORD comparison of amorphane-I isolated from the hydrogenation products of zizanene[7] and (+)—I (from HCO_2H treatment of (+)-δ-cadinene).

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[6] Ohta, Y. and Hirose, Y. (1969) *Tetrahedron Letters* 1601.
[7] Andersen, N. H. (1970) *Tetrahedron Letters* 4651.
[8] Andersen, N. H. and Falcone, M. S. (1969) *J. Chromatog.* **44**, 52.
[9] Andersen and Syrdal, D. D. (1970) *Phytochem.* **9**, 1325.
[10] Charney, E., Ziffer, H. and Weiss, U. (1965) *Tetrahedron* **21**, 3121.
[11] Andersen, N. H. and Svedberg, D. unpublished work.
[12] Andersen, N. H., Falcone, M. S. and Syrdal, D. D. (1970) *Tetrahedron Letters* 1759.

Biogenetic Significance

The position of the double bonds in these cadalene sesquiterpenes argues against their production from germacrenes as is the usual case for cadinene, muurolanes, etc.[13] They probably represent the cyclization products of bisabolenes and curcumenes, when they are true natural products. In other cases, they likely result from isomerization of normal cadinenes under the oil isolation conditions. It is worth noting that the two isomers from *Alpinia officinarium* retain the same absolute stereochemistry at C-10. Curiously, Alaska cedar produces (—)-I (the 10β-CH_3 isomer) even though its oil is rich in (—)-curcumenes (α-CH_3 series) and (—)-calamenene (10α-CH_3). In fact, the only correlation of β-CH_3 stereochemistry in this oil is (—)-I and β-alaskene which elute as a single peak on gas chromatography. The variable optical purity of these dienes in nature is not unexpected considering the multiple pathways by which they could be produced in any particular plant oil.

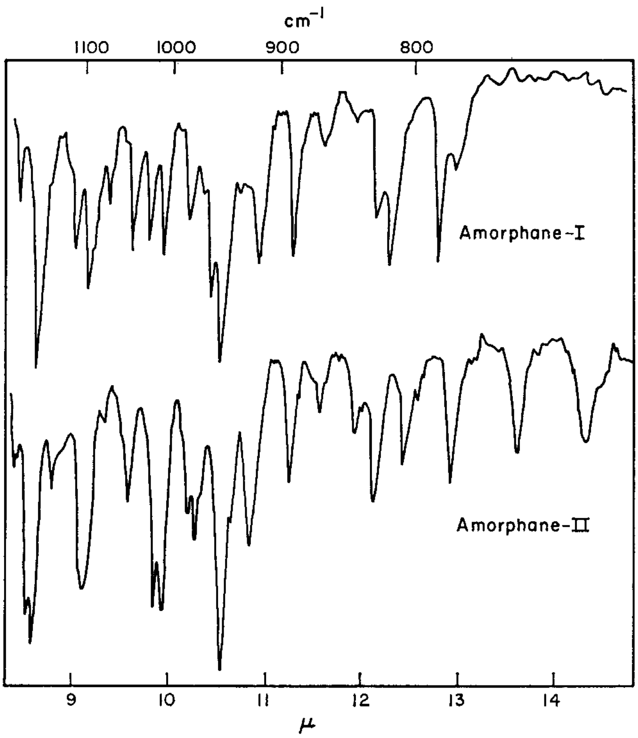

FIG. 2. FINGERPRINT REGION IR SPECTRA OF AMORPHANES-I AND -II.

EXPERIMENTAL

Analytical and preparative GLC was carried out as previously described.* Retention data were evaluated in the form of self-consistent Kovats indices (see Ref. 8). Chromatography on $AgNO_3$-impregnated

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* See Refs. 15 and 16 for details.

[13] YOSHIHARA, K., OHTA, Y., SAKAI, T. and HIROSE, Y. (1969) *Tetrahedron Letters* 2263.

alumina was performed according to the method of D.D.S.[14] or as previously described.[15,16] In particularly difficult separations, the dry column technique was employed (300 g 15% $AgNO_3$–Al_2O_3 per g olefin mixture, cyclohexane as eluent) with prior activation of the adsorbent at 130° for 72 hr. Dehydrogenations were performed and analyzed according to Refs. 3 and 4. All hydrogenations were done using Adam's catalyst in acetic acid. UV spectra were taken in methanol or ethanol. CD spectra were recorded as *ca.* 0·2–2·0 mM solutions in pentane (l. = 1 mm) on a Cary 6001.

Isolation of sesquiterpenes from essential oils. Diene V was obtained as a dehydration product of cubenol[17] and gave the expected spectral data. *Diene VI*, isolated from the oil of *Piper cubeba* using techniques previously described,[15,16] was assigned the given structure based on the NMR spectrum and chemical evidence. *Epizonarene*, (−)-I. Alaska yellow cedar leaf oil[9] was fractionated *in vacuo*. A 10-g sample of the sesquiterpene fraction (b.p. 115–125°, 25 mmHg) was chromatographed on 220 g 15% $AgNO_3/Al_2O_3$ using a cyclohexane–benzene gradient. The later cyclohexane fractions contained α- and β-alaskene together with diene (−)-I. Repeated chromatography of this fraction afforded (in order of elution): α-alaskene ($[\alpha]_D$ −88°),* β-alaskene ($[\alpha]_D$ − 18°),* and 10-epizonarene:* $C_{15}H_{24}$; MS *m/e* 204·183 (P), 161 (base); other spectral data (see Table 1, Fig. 1). *Zonarene* (II), *calamenene* (III) and (+) *-δ-cadinene* (IV) *from cade oil.* Commercial cade oil was freed of phenolics (15% aq. NaOH) and distilled. A 5-g portion of the high-boiling sesquiterpene fraction (b.p. 128–135°, 20 mm) was chromatographed on 15% $AgNO_3$–Al_2O_3 giving calamenene, dihydro-α-curcumene, zonarene, δ-cadinene, calcorene, α-muurolene, and several unknown constituents. (−)-zonarene, thus obtained was still impure as judged by the low $\Delta\epsilon$ value—the spectral data appear in Table 1. The MS confirmed the molecular formula and was otherwise similar to that of epizonarene. *Zonarene* (II) *and* (+)-*epizonarene* (I) were isolated from the oil of *Alpinia officinarium*[18] using techniques previously described.[15,16] Their IR spectra appear in Fig. 1. In the course of studies of the constituents of *Zingiber officinale*, *Pelargonium graveolens*, *Pimenta diocia*, *Eugenia caryophyllus*, and *Laurus noblis* using $AgNO_3$–Al_2O_3 chromatography followed by preparative GLC, fractions displaying the characteristic IR and UV spectra of zonarene were isolated. Ginger oil also yielded *epi*-zonarene, identified in the same manner. The rotatory properties of these samples were not investigated.

	$I_A^{155°}$	$I_A^{190°}$	$I_C^{165°}$	$I_D^{160°}$	$I_F^{170°}$
Calamenene	1548	1567	1809	2085	1524
α-Copaene	1410	1433	1551	1665	1400·5
α-Alaskene	1539	1557	1763·5	1938·5	
β-Alaskene	1520·5	1539	1738	1906·5	
10-Epizonarene	(~1519)	1538	(1739?)	1905	
Zonarene	(~1547)		1781	1965	
δ-Cadinene	1547		1782·5	1960	(1526·5)
Diene (V)	(1368?)		(1506?)		
α-Curcumene	1484		1787·5	1992·5	1480·5
α-Calcorene		1590	1926	2189	
α-Muurolene	1531	1548	1753	1928·5	1508
Diene (VI)					
γ-Cadinene	1555	1573	1792	1978·5	1523·5

Chromatographic retention data for sesquiterpenes. The sesquiterpenes encountered during the study of the zonarenes are listed in the order of their elution from $AgNO_3$–Al_2O_3. The retention indices are calculated according to Ref. 8 and refer to the following phases (A, Apiezon L; C, Carbowax 20M; D, DEGS; and F, Silicone SF-96) at the indicated temperatures.

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* Final spectral data were obtained on samples that were collected from a Carbowax preparative GLC column and then passed through basic alumina (Woelm, Activity I) with pentane.

[14] Syrdal, D. D. (1971) Sesquiterpenes of *Chamaecyparis nootkatensis*: I, Isolation and structure determination: II, absolute stereochemistry; III, chemical simulation of biogenesis, Thesis, University of Washington, Seattle, U.S.A.

[15] Lawrence, B. M., Hogg, J. W. and Terhune, S. J. (1970) *J. Chromatog.* **50**, 59.

[16] Lawrence, B. M. (1971) *Can. Inst. Food Technol. J.* A44.

[17] Ohta, Y. (1966) Structural study on sesquiterpenoids, cubebenes and cubenols from Cubeb oil, Thesis, Institute of Food Chemistry, Osaka, Japan.

[18] Lawrence, B. M., Hogg, J. W. and Terhune, S. J. (1969) *Perfum Essent. Oil Rec.* **60**, 88.

Acid-catalyzed isomerization studies. The formic acid isomerization of (+)-*δ-cadinene.* δ-Cadinene (350 μl) was dissolved in 6 ml of *n*-decane with stirring. The resulting solution was added to 4 ml of 98+ % formic acid and the resulting mixture was stirred at 100° in a flask sealed with a serum cap. Aliquots were analyzed on stationary phase D at 160°. After 5 hr, the products were isolated by the addition of hexane followed by washing with water. Peaks 1, 2 and 3 were collected from a Carbowax 20M preparative gc column (150°) and proved to be: (a) α-ylangene ($I_D^{160} = 1653{\cdot}5$, $I_A^{190°} = 1426$); (b) ($I_D^{160°} = 1824$; two peaks on carbowax and Apiezon-L, $I_A^{190°} = 1499, 1506{\cdot}5$); and (c) (+)-10-epizonarene ($I_A^{190°} = 1537$).

Peak	$I_D^{160°}$ (cmpd.)	Time (hr)						
		0·0	0·5	1·0	1·8	3·0	4·0	5·0
1	1651		1	1	5	7	8	10
2	1823·5		1	5	15	25	32	35
	1875		1	2	6	10	15	15
3	1905 (Epizonarene)	5	10	22	40	40	40	45
	1961 (δ-Cadinene)	90	85	65	35	20	10	8
	1996		0	5	5	4	3	2
	2082 (Calamenene)		1	1	2	3	5	5

Reactions in aqueous dioxane. The olefins were dissolved in 4:1, dioxane–H_2O which was 0·012–0·015 N in HCl. The reaction mixtures were maintained at 50–80° for the indicated times and analyzed by GC.

Trifluoroacetic acid treatment of epizonarene. Crude epizonarene (5 μl, containing *ca.* 30% β-alaskene, ex. Alaska cedar) was added to 100 μl each of decane and TFA. After 1 hr stirring, 10 ml of pentane was added and the resulting solution was washed repeatedly with water. Preparative gc on Apiezon-L followed by Carbowax 20M afforded 1·1 mg *calamenene* (III)—59% cis by NMR, UV (CD): 278 (720, +0·112), (720, +0·112), 270 (627, +0·071), and 264 nm ε 414, Δε +0·037).

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