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THE ABSOLUTE STEREOCHEMISTRY OF THE CALAMENENES

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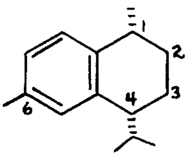
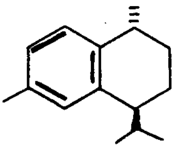
In the course of a study of the sesquiterpenes of the leaf oil of Alaska Cedar (Chamaecyparis nootkatensis)[1] we encountered a levorotatory calamenene which was clearly a mixture of the cis- and trans-isomer by NMR (see Figure). This mixture could not be resolved into its components by any of six glc stationary phase used by us (each in columns with more than 20,000 theoretical plates) nor by careful chromatography on highly-activated $AgNO_3$-Al_2O_3. A careful search of the literature on calamenene revealed that the diastereomer question had only rarely been considered and that the relative and absolute stereochemistry of the commonly isolated (-)-calamenene were not known.[2] It had been suggested that (-)-calamenene had a β-oriented isopropyl since khusinol (V) affords a dextrorotatory calamenene on treatment with $BF_3 \cdot Et_2O$,[3] and further that the natural material is the cis-isomer.[3,4] However the evidence was not compelling on these points as there was no assurance that the rotation comparisons were made on the same diastereomer. An attempt to resolve the problem by synthesis starting with menthone had this difficulty as well as several synthetic stages at which epimerization was possible.[3]

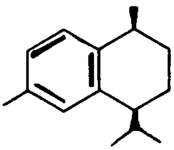
We report here some of our studies on natural calamenenes and the synthesis of calamenenes from sesquiterpenes of known absolute stereochemistry which allows us to assign cis structure I to the major calamenene from Alaska Cedar and trans structure II to the common natural calamenene. In addition analysis of the CD cotton effects of these mixtures and a comparison with the isocalamenenes (IV, see preceding communication) has led us to a rule for predicting the sign and relative magnitude of the ^1L_b band dichroism of tetralins. What follows is not the circuitous route by which we arrived at the assignment, but rather the most direct path from a selection of data to the conclusions.



I $[\alpha]_D = -22°$, $\Delta\varepsilon_{278} = +0.20$



II $[\alpha]_D = -96°$, $\Delta\varepsilon_{278} = +0.96$



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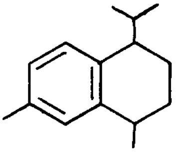

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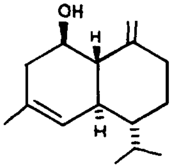

V

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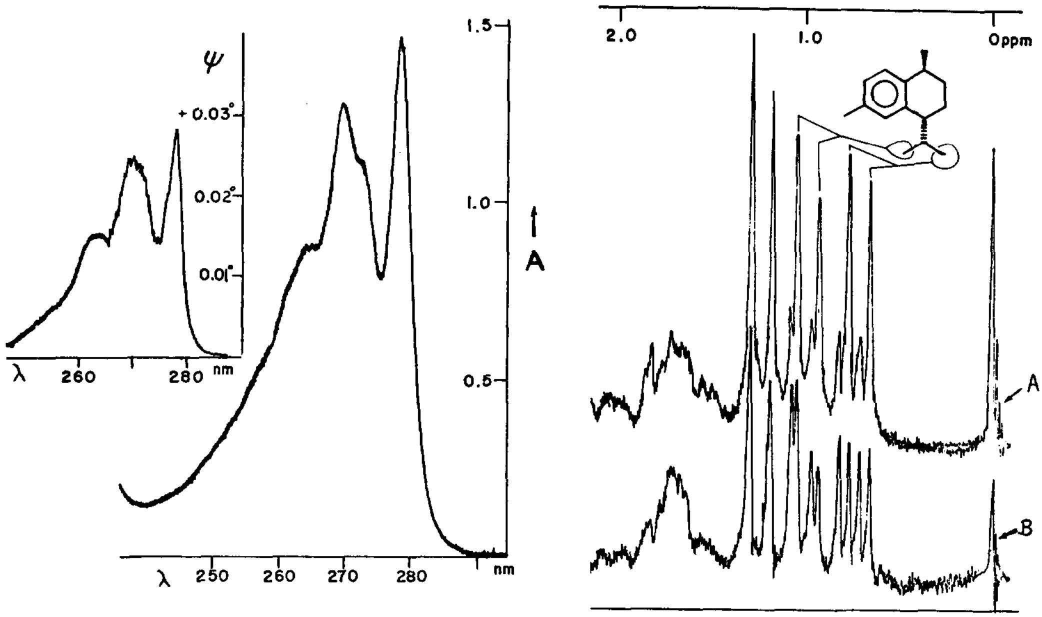
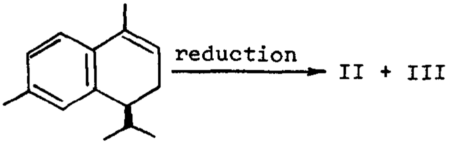
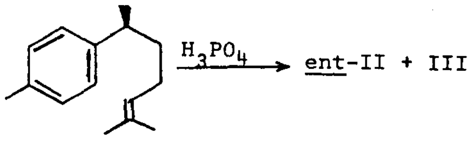
Figure: CD and UV Spectra of a levorotatory calamenene mixture; 60 MHz NMR of calamenenes: A - ex Cade Oil (71% upfield, trans, isomer), B - a 1:1 mixture of cis- and trans-calamenene.



Since no method we could devise allowed a separation of the calamenene diastereomers we had to rely on spectroscopic data on mixtures. The NMR spectra were used to determine the diastereomeric ratio from the relative heights of the isopropyl doublets (see Figure), the upfield set of doublets corresponding to the natural calamenene of Cade Oil (now known to be trans). The table (next page) gives the result of such determinations together with the CD data. The reduction of (+)-α-calcorene (VI)[5] was studied in order to obtain the diastereomers with the β-isopropyl group absolute configuration preserved in both. Initially we hoped to obtain the trans-isomer by metal-ammonia reduction due to kinetic axial protonation of the intermediate benzylic anion and the cis-isomer by hydrogenation. The low stereoselectivity observed (see Table entries 5 and 6) did not allow us to assign the relative stereochemistry, however comparison of compositions and Δε-values allowed us to calculate the Δε-values for the individual diastereomers.[6] This calculation revealed that the absolute configuration of the methyl substituent determined the sign of the CD cotton effect. The Δε-values and $[\alpha]_D$-values so obtained are shown under structures I and II. It then remained to determine the relative stereochemistry. Since it was established that the methyl group configuration determined the sign of the CD at 278 nm, a CD measurement on a calamenene mixture which was homogeneous with



VI $\Delta\varepsilon_{269}$ = +1.05



VII

Source of Calamenenes		trans/cis-ratio	$\Delta\varepsilon_{278}$[a] observed	$\Delta\varepsilon_{278}$[a] calc'd	Basis for Calculation
1) Cade Oil		71:29	+0.61[5]	+0.62[4]	II:III
2) Cuppressus		78:22	+0.64[5]	+0.65[7]	II:III
3) Alaska Cedar		27:73	+0.44	+0.41	II:I
4) (+)-δ-cadinene $\xrightarrow{CF_3CO_2H}$		45:55	+0.25[2]	+0.32	II:III
5) (+)-Calcorene $\xrightarrow[(\phi_3P)_3RhCl]{H_2}$		64:36	+0.54[4]	-	II:III
6) (+)-Calcorene $\xrightarrow{LiNH_3}$		57:43	+0.46[2]	-	II:III
7) (+)-α-curcumene $\xrightarrow{H_3PO_4}$	at 80°	71:29	-0.069	-ve	(see text)[7]
	at 25°	74:26	-0.082	-ve	

a) $\Delta\varepsilon_{278}$ are corrected to ε_{278} = 750 from UV spectra of each sample in order to minimize measurement errors. All calamenene samples were free of other hydrocarbon by glc and had been purified by a preparative glc on a polar and non-polar phase prior to filtration through alumina (Woelm I, basic).

respect to the absolute configuration at the methyl substituent could be used for this assignment. Dextrorotatory α-curcumene was found to cyclize to calamenene in 80% yield in phosphoric acid (entry 7). Although extensive racemization occurs before cyclization[7], to the extent that optical activity is retained the expected products are III and the enantiomer of II.[7] The negative ^1L_b band observed in the CD of this mixture indicates that the minor isomer from the reduction of calcorene must be the *cis*-isomer.[7] In addition the relative chemical shifts observed support this assignment when the anisotropic effect of the aromatic ring is considered.* As an illustration of the correctness of the calculated Δε-values and assignments these values have been used to calculate Δε-values for the various isolated calamenenes and that produced from δ-cadinene on treatment with trifluoracetic acid. The agreement between calculated and observed Δε is very good and leaves us with no doubt concerning the assignments used for the calculation. Thus the major calamenene of Alaska Cedar bears an α-isopropyl group—both isomers being homogeneous with respect to absolute stereochemistry at C-1. The low Δε in the case of the calamenene from (+)-δ-cadinene suggests some degree of prior equilibration with an isomer with a $\Delta^{6,7}$, olefinic linkage.[8]

Finally these assignments, together with the data from the isocalamenenes, point to a consistent explanation of the factors governing the tetralin ^1L_b-band Cotton effect.[9] A biased sector rule[10] which correctly predicts both sign and magnitude is shown below together with the summarized CD data. The conformations are assigned from NMR.* The positive CD of the *trans* isomers is ascribed to the benzylic bonds within the ring ("ring chirality")—the reduced magnitude of the *trans*-isocalamenene (B) reflects the greater bond polarity of the benzylic bond from C-1 to the more polarizable isopropyl substituent. The negative band of the *cis*-isomers is ascribed to the C-1→C-2 bond contribution. In this case, the calmenene (D) has the lower

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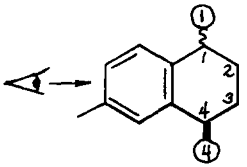
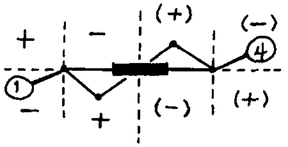
* The trans-isomers are assumed to exist in the M-helicity twist-chair (TC) with both substituents pseudoequatorial. The chemical shift of the benzylic-CH_3 (δ 1.24 ± 0.01 ppm) in each of the four compounds indicates a similar disposition in the *cis* isomers. The skewed boat conformations suggested by this analysis are consistent with the downfield position of the iPr signals in the *cis*-isomers.

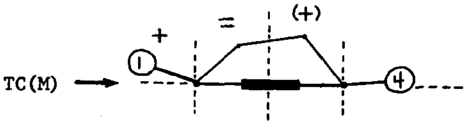
magnitude due to the opposing contributions the bond to the C-1 substituent and the ring bond along the minor axis.



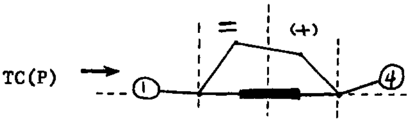
	④	①	Δε
A	iPr	αCH_3	+0.96
B	CH_3	αiPr	+0.55
C	CH_3	βiPr	-0.41
D	iPr	βCH_3	-0.20



M-helicity TC of trans-compounds (A and B) with sector signs



for cis-calamenene (D)



For cis-isocalamenenene(C)

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REFERENCES

1. N. H. Andersen and D. D. Syrdal, Phytochemistry, 9, 1325 (1970).

2. (-)-Calamenene is shown as the trans-isomer in E. Klein and W. Rojahn's recent work "Die Konfigurationen der Sesquiterpenoide." The basis is, apparently, the conversion of cubenol to calamenene. However, the trans relationship of the methyl and isopropyl groups in cubebene-related compounds is not firmly established, resting essentially on the assumption that $SOCl_2$ dehydration of a tertiary alcohols requires an adjacent trans-hydrogen.

3. P. H. Ladwa, G. D. Joshi, and S. N. Kulkarni, Chem. Ind., 1601 (1968).

4. J. W. Rowe and J. K. Toda, Chem. Ind., 922 (1969).

5. The absolute stereochemistry of (+)-α-calcorene is based on its co-occurrence with cadalane sesquiterpenes bearing a β-isopropyl group. The positive CD band which we observed for the styrene absorption confirms this assignment. For applications of the "skewed styrene rule" see: P. Crabbe in Topics in Stereochemistry, 1, 93 (1967); and W. L. Bencze, B. Kisis, R. Puckett, and N. Finch, Tetrahedron, 26, 5407 (1970).

6. The Δε-values were obtained by simultaneous solution of two equations in two unknowns.

7. Calamenene mixtures were found to be unchanged (isomeric composition and Δε-value) by the cyclization media after prolonged exposure at either 80° or 140°C. and α-curcumene recovered from reactions of shorter duration was partially racemized. (A referee has pointed out that the cis/trans assignment must be considered as tentative until it can be proven that neither the cis nor the trans product is formed with a net excess of inversion at the methylated center.

8. A 4,6-cadinadiene is, in fact, produced from δ-cadinene in high yield with non-oxidizing acids.

9. The rule of J. Brewster and J. G. Buta [J. Am. Chem. Soc., 88, 2233 (1966)] does not offer an explanation using either this or the alternate cis/trans assignment.

10. The sector rule presented here is identical to that proposed by G. Snatzke for 6-substituted-tetralins with respect to the signs assigned to the sectors. It differs only in assigning a greater role to the benzylic bonds emanating from the major axis. See "Circular Dichroism: Chiroptical Properties of the Benzene Chromophore," presented by G. Snatzke at the XXIIIrd IUPAC Congress (July 1971). We thank Dr. Snatske for a preprint of his manuscript.