Public Health Service for financial support through NIH Research Grant AI 11728. The services of the Purdue University Biological Magnetic Resonance Laboratory (provision of high-field NMR spectra) and the Los Alamos Stable Isotope Resource (supply of ^{13}C-labeled material), supported under NIH Division of Research Resources Grants RR 01077 and RR 00962, respectively, are gratefully acknowledged.

Registry No. 1, 34524-20-4; 2, 61230-25-9; 3, 70658-70-7; [2-^{13}C]acetic anhydride, 77257-01-3; [2-^{13}C]bromoacetic acid, 64891-77-6; [2-^{13}C]malonic acid, 55514-11-9; D-[2-^{2}H]valine, 77257-02-4; L-[2-^{2}H]valine, 77257-03-5.

Transannular Cyclization of a *trans*-1(10)-*cis*-4-Germacradiene[1a]

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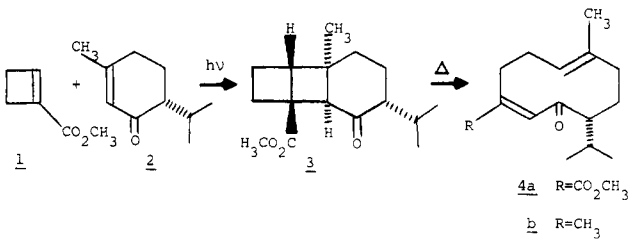
New biomimetic cyclization of the *trans*-1(10)-*cis*-4-germacradiene **4a** by using acetic acid in thiophenol afforded the cadinane **5** and the eudesmanes **6a,b** and **7**. The structure of each product was determined by spectral analysis, and the absolute configuration of **7** was determined by X-ray crystallography.

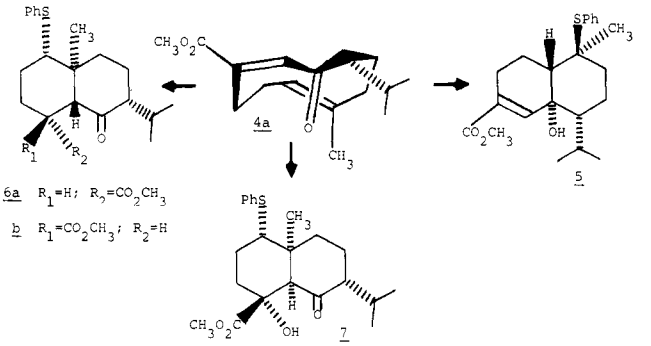
Many sesquiterpenes have been shown to be biogenetically derived from germacranes,[2] and the conversions of these 1,5-cyclodecadiene derivatives to cadinane, guaiane, and eudesmane sesquiterpenes have been the subject of several reports.[3] We felt it would be interesting to study the intramolecular cyclization reactions of the readily available synthetic *trans*-1(10)-*cis*-4-germacradiene **4a** which was synthesized in two steps from the optically active monoterpene (−)-piperitone (**2**)[1a] (Scheme I).

Treatment of **4a** with acetic acid in thiophenol gave a mixture of four isolated products which included the cadinane **5** and the three eudesmanes **6a,b** and **7** (Scheme II). The structure of the cadinane **5** was determined by the comparison of its proton and ^{13}C NMR spectra with similar synthetic and natural cadinane-type compounds (see Table I).[1] The structures of the three isomeric eudesmane products were more difficult to assign. We decided it would be useful to determine the structure of the most complex isomer **7** by X-ray crystallography. Crystal data are given in the Experimental Section. Figure 1 is a stereoscopic view of the eudesmane **7** which shows that it has a *cis*-decalone structure which contains a PhS group at C-1 and a hydroxyl group at C-4. The absolute configuration of **7** depicted in Figure 1 was determined by the anomalous scattering of the sulfur atoms and was established by refining both enantiomers. The final weighted R values were 0.0415 for the configuration shown and 0.442 for its antipode. Thus, by Hamilton's test,[4] the structure shown for **7** represents the correct absolute stereochemistry. Tables II–VI list final atomic and final anisotropic thermal parameters, bond angles, and selected torsion angles and are available as supplementary material.

Scheme I



Scheme II



The structures of **6a** and **6b** were determined by a detailed study of their proton and ^{13}C NMR spectra and by comparison to **7** and similar compounds.[3b,5]

The chemical shift of C-10 in **6a** and **6b** was considerably downfield from the chemical shift of C-10 in **7** and 10-epijunenol.[5b] This showed that the ring juncture in **6a** and **6b** was trans. A study of the molecular model of the most stable conformation of the *trans*-1(10)-*cis*-4-germacradiene **4a** and those of the products **6a** and **6b** showed that thiophenol would preferentially attack the C-1(10)-*trans*-olefin from the bottom face and would close the ring to give a *trans*-decalin and an α-axial ester at C-4, compound **6a**. The basic workup of the reaction then caused the α-axial ester at C-4 to epimerize to the thermodynamically more stable β-equatorial isomer, compound **6b**. This was confirmed by treatment of both **6a** and **6b** with

(1) (a) For the previous paper in this series see: Williams, J. R.; Callahan, J. F. *J. Org. Chem.* **1980**, *45*, 4479. (b) Temple University. (c) Hoffmann-LaRoche, Inc.

(2) (a) Herz, W. *Isr. J. Chem.* **1977**, *16*, 32. (b) Geissman, T. A. *Recent Adv. Phytochem.* **1973**, *6*, 65. (c) Fischer, N. H.; Oliver, E. J.; Fischer, H. D. *Fortschr. Chem. Org. Naturst.* **1979**, *38*, 47.

(3) (a) Herout, V.; Suchý, M.; Sorm, F. *Collect. Czech. Chem. Commun.* **1961**, *26*, 2612. (b) Sorm, F.; Dolejs, L. In "Chimie des Substances naturelles"; Lederer, E., Ed.; Hermann: Paris, 1966. (c) Sutherland, J. K. *Tetrahedron* **1974**, *30*, 1651. (d) Niwa, M.; Iguchi, M.; Yamamura, S. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3148. (e) Niwa, M.; Iguchi, M.; Yamamura, S. *Ibid.* **1976**, *49*, 3137. (f) Doskotch, R. W.; El-Feraly, F. S. *J. Org. Chem.* **1970**, *35*, 1928. (g) Doskotch, R. W.; Hufford, C. D.; El-Feraly, F. S. *Ibid.* **1972**, *37*, 2740. (h) Tada, H.; Takeda, K. *Chem. Pharm. Bull.* **1976**, *24*, 667. (i) Kodama, M.; Yokoo, S.; Matsuki, Y.; Ito, S. *Tetrahedron Lett.* **1979**, 1687. (j) Tasankova, E.; Ognyanov, I.; Norin, T. *Tetrahedron*, **1980**, *36*, 669.

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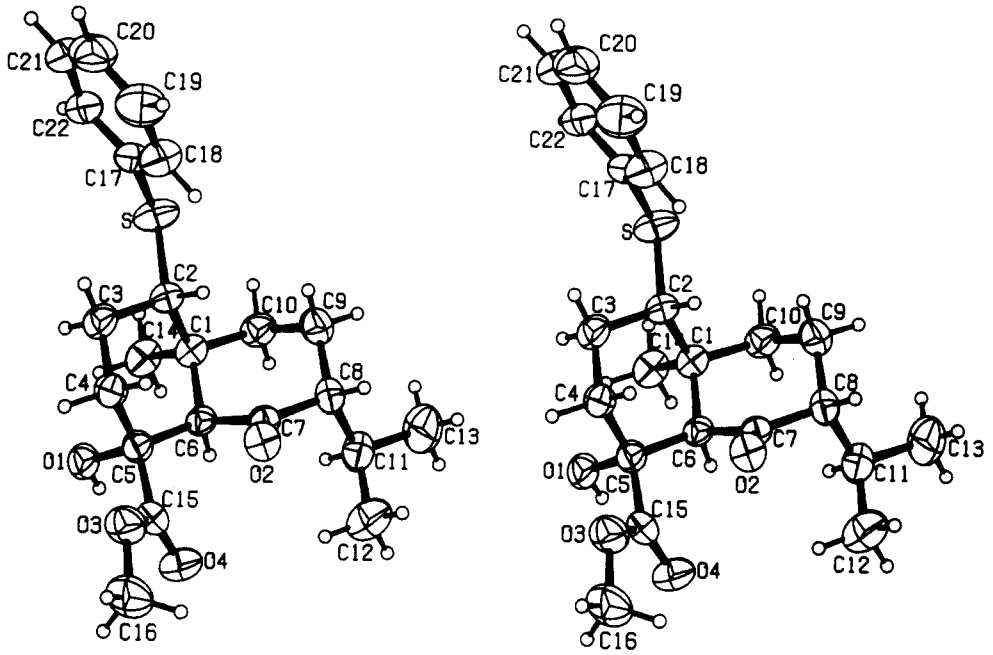


Figure 1. Stereoscopic view of 7.

Table I. Carbon-13 NMR Data of Thiophenol Cyclization Products[a]

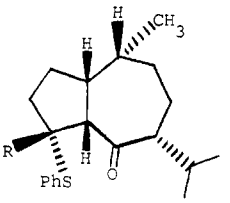
	compd			
carbon	5	6a	6b	7
1	47.8	54.2	51.4	53.2
2	18.3	23.7	23.9	25.7
3	25.5	26.4	29.3	44.1
4	132.1	39.1	37.4	74.7
5	140.0	54.2	55.6	60.2
6	72.9	212.4	212.8	214.8
7	49.0	56.6	57.4	58.2
8	18.5	22.6	22.4	23.1
9	40.3	31.9	32.0	30.5
10	54.4	42.9	43.7	34.3
11	25.2	27.3	28.1	28.5
12	23.8	20.9	20.5	20.4
13	18.5	19.6	20.1	20.2
14	20.9	23.5	22.6	24.4
15	167.9	174.9	174.1	173.8
OMe	51.6	51.5	51.1	51.8
A	131.2	135.4	134.9	135.1
B	137.7	132.2	132.2	132.2
C	128.6	128.8	128.7	128.9
D	128.3	126.8	126.9	126.9

[a] Aromatic residue is numbered

refluxing sodium methoxide in methanol. Treatment of **6a** under these conditions followed by esterification with diazomethane gave **6b** while treatment of **6b** under the same conditions had no effect, and **6b** was recovered unchanged.

The formation of the cadinane **5** could be rationalized by the following mechanism. Protonation of the C-6 ketone in **4a** followed by attack of thiophenol at C-10 would give the cadinane **5**. The formation of the minor product **7** could not be easily rationalized. It is obvious that an oxidation occurred somewhere in the reaction pathway, and this could have been caused by oxygen present in the reaction mixture or by the workup conditions.

It was interesting to note that none of the expected guaiane isomer **8a** was isolated as was the case in the cyclization of isoacoragermacrone **4b** which yielded **8b** under similar conditions.[3b] However, the reaction was useful since the eudesmanes **6a,b** and **7** can be considered precursors for a number of eudesmane natural products, including acolamone[3b] and 10-epijunenol.[5b]



8a R=CO_2CH_3

b R=CH_3

Experimental Section

Melting points were taken with a Thomas-Hoover apparatus and are uncorrected. IR spectra were taken with a Perkin-Elmer 137 Infracord spectrophotometer. ^{13}C NMR spectra were recorded at 25.16 MHz on a Varian XL-100 spectrometer fitted with a Nicolet 1180 pulse system, and ^1H NMR spectra were recorded at 90 MHz on a Perkin-Elmer R-32 spectrometer. Chemical shifts are reported in δ units from the internal standard Me_4Si in chloroform-*d*. Low-resolution mass spectra were taken with a Hitachi Perkin-Elmer RMU-6H. High-resolution mass spectra were taken with a Hitachi Perkin-Elmer RMH-2. TLC was carried out on silica gel GF plates and column chromatography was performed by using Woelm silica gel.

Cyclization of 4a. A solution of **4a**[1a] and acetic acid (3.0 mL) in thiophenol (7 mL) was stirred at room temperature for 48 h. The solution was then diluted with ether and washed with 2.5 M NaOH. The combined ether extracts were dried over anhydrous $MgSO_4$ and evaporated. Purification by silica gel chromatography gave four isomeric products which are listed in the order of their elution.

For eudesmane **6a**: IR (neat) 1725, 1715 1618 cm^{-1}; NMR δ 7.50–7.15 (m, 5 H), 3.64 (s, 3 H), 3.30–2.80 (m, 3 H), 1.11 (s, 3 H), 0.94 (d, 3 H, J = 6 Hz), 0.87 (d, 3 H, J = 6 Hz); mass spectrum, m/e (relative intensity) 374 (M^+, 86), 233 (66), 205 (100), 177 (32), 107 (27), 93 (46), 69 (41); calcd for $C_{22}H_{20}O_3S$ m/e 374.1916, found m/e 374.1930.

For cadinane **5**: IR (neat) 3482, 1716, 1643 cm^{-1}; NMR δ 7.60–7.15 (m, 5 H), 7.09 (br s, 1 H), 3.73 (s, 3 H), 1.39 (s, 3 H), 0.96 (d, 3 H, J = 7 Hz), 0.90 (d, 3 H, J = 7 Hz); mass spectrum,

m/e (relative intensity) 374 (M^+, 2), 233 (75), 145 (25), 131 (25), 109 (100), 105 (50), 93 (38), 91 (75); calcd for $C_{22}H_{30}O_3S$ m/e 374.1916, found m/e 374.1930.

For eudesmane **6b**: mp 105 °C; IR (KBr) 1728, 1702, 1583 cm^{-1}; NMR δ 7.57–7.13 (m, 5 H), 3.78–3.50 (m, 1 H), 3.59 (s, 3 H), 3.20–2.80 (m, 2 H), 1.22 (s, 3 H), 0.96 (d, 3 H, J = 7 Hz), 0.84 (d, 3 H, J = 7 Hz); mass spectrum, m/e (relative intensity) 374 (M^+, 28), 233 (100), 205 (15), 109 (13), 107 (17), 93 (24), 91 (15); calcd for $C_{22}H_{30}O_3S$ m/e 374.1916, found m/e 374.1931.

For eudesmane **7**: mp 175–176 °C; IR (KBr) 3380, 1725, 1690, 1586 cm^{-1}; NMR δ 7.50–7.15 (m, 5 H), 3.64 (s, 3 H), 3.11 (s, 1 H), 3.05–2.80 (m, 1 H), 1.47 (s, 3 H), 0.96 (d, 3 H, J = 6.8 Hz), 0.84 (d, 3 H, J = 6.8 Hz); mass spectrum, m/e (relative intensity) 390 (M^+, 15), 221 (100), 110 (35), 109 (75), 95 (30), 91 (35), 69 (50); calcd for $C_{22}H_{30}O_4S$ m/e 390.1865, found m/e 390.1894. The total overall yield was 61% of the mixture of the four isomers **5**, **6a**, **6b**, and **7** in the ratio of 23:10:49:18, respectively.

X-ray Analysis. Single crystals of the eudesmane **7** were prepared by slow crystallization from methanol. The crystals were orthorhombic, space group $P2_12_12_1$, with a = 10.148 (2) Å, b = 14.023 (2) Å, c = 14.721 (2) Å, and d_{calcd} = 1.238 g cm^{-3} for Z = 4 ($C_{22}H_{30}O_4S$, mol wt 390.54). A crystal measuring approximately 0.30 × 0.30 × 0.40 mm was used for data collection. The intensity data were measured on a Hilger-Watts diffractometer (Ni-filtered Cu K radiation, θ–2θ scans, pulse-height discrimination) and were corrected for absorption (μ = 15.3 cm^{-1}). A total of 1629 reflections were measured for $\theta < 57°$, of which 1579 were considered to be observed [$I > 2.5\sigma(I)$]. The structure was solved by a multiple-solution procedure[6] and was refined by full-matrix least-squares methods. Three reflections which were strongly affected by extinction were excluded from the final refinement and difference map. In the final refinement anisotropic thermal parameters were used for the nonhydrogen atoms, and isotropic temperature factors were used for the hydrogen atoms. The hydrogen atoms were included in the structure factor calculations, but their parameters were not refined. The final discrepancy indices are R = 0.032 and R_w = 0.042 for the remaining 1576 observed reflections. The final difference map has no peaks greater than ±0.2 e $Å^{-3}$. The absolute configuration of **7** depicted in Figure 1 was determined by the anomalous scattering of the sulfur atoms and was established by refining both enantiomers. The final weighted R values were 0.0415 for the configuration shown and 0.442 for its antipode.[4]

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Epimerization of the Eudesmane 6a. To a solution of sodium (0.10 g) in methanol (5 mL) was added the eudesmane **6a** (0.020 g, 0.053 mmol), and the subsequent mixture was refluxed for 20 h. The methanol was removed under reduced pressure, and the residue was diluted with water and acidified. This aqueous mixture was then extracted with ether, and the ether extracts were dried (anhydrous $MgSO_4$) and evaporated. The crude residue was then treated with ethereal CH_2N_2, and the resulting product was shown to be identical with **6b** by ^1H NMR.

Similar treatment of **6b** resulted only in recovered **6b**. None of the isomeric **6a** was found.

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Registry No. 4a, 74878-02-7; **5**, 77462-50-1; **6a**, 77462-51-2; **6b**, 77519-46-1; **7**, 77462-52-3.

Supplementary Material Available: Tables II–VI containing final atomic parameters, final anisotropic thermal parameters, bond lengths, bond angles and torsion angles, respectively, for **7** (6 pages). Ordering information is given on any current masthead page.

N-[(Carbobenzyl)oxy]-Δ^E-phenylalanine Ethyl Ester

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Received December 2, 1980

The synthesis of the title compound (**1a**) has been accomplished by rearrangement of a vinylic isocyanate, and its configuration was confirmed by X-ray crystallography. The configurational stability of **1a** to both acids and bases was investigated, and the NMR "rules" developed by other workers in the dehydro amino acid field were checked. It was concluded that an (*E*)-dehydrophenylalanine residue will probably not survive the standard methods of peptide synthesis.

In most of the recent work directed toward the synthesis of biologically important dehydropeptides,[1] only the thermodynamically stable isomer (*Z* configuration) of the dehydro amino acid residue has been incorporated. Since the configuration of the double bond in the dehydro residue may control the conformations of several proximal amino acid residues and will afford information on conformations acceptable to the bioreceptor, it is important that we be able to incorporate *both* double bond isomers into bioactive peptides. To this end we have synthesized (*Z*)-Δ^E-PheOEt (**1a**) by a new method and studied its thermal and chemical stability to reagents used in peptide synthesis.

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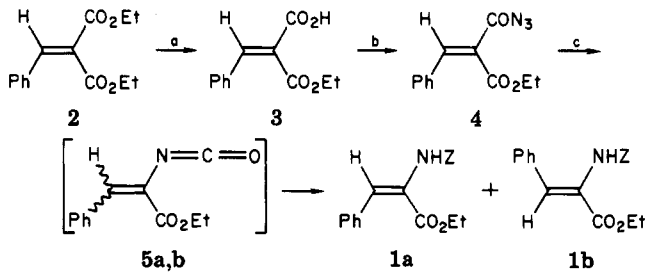
Scheme I[a]



[a] (a) 1 equiv of KOH/ethanol; H_3O^+; (b) $[(CH_3)_2CH]_2NC_2H_5$, EtOCOCl, acetone, −5 °C, NaN_3/H_2O; (c) $PhCH_2OH$, 100 °C.

Scheme I shows the synthesis of (*Z*)-Δ^E-PheOEt (**1a**) from the known[2] monoacid **3**. This compound has the

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