was concentrated to a minimum volume in vacuo, and then the solution's pH was adjusted to 7.5 with a solution saturated with barium hydroxide. Ethanol (2 volumes) was added, and the resulting precipitate was filtered off and washed with ethanol and then ether. This barium salt was deionized with Dowex 50 (H^+) to give the free acid. However, under no conditions could the free acid (or its ammonium salt) be induced to crystallize.

The R_f values of product 11 were (Whatman no. 1, descending): system A 0.24; system B 0.45; system C 0.64. The relative mobility on paper electrophoresis [Whatman no. 1, 0.05 M $HCOONH_4$ (pH 3.5), 30 V/cm] was: UDP/UMP/11 = 1:0.59:0.57. UV λ_{max} (ϵ) pH 1 237 (9380) and 302 (10 580), pH 12 321 nm (14 560). Extinction coefficients were based on inorganic phosphate determination after washing with mixed acids.

This product gave a positive periodate–benzidine color test (yellow-white spot on blue background): ^1H NMR (D_2O) 5.81 (1, d, H1'); 9.20 (1, s, H6). A satisfactory C, H, and N analysis cound not be obtained for the barium salt. Anal. Calcd for $C_9H_9N_3O_{11}PBa_{1.5}\cdot 2H_2O$: N, 6.91; P, 5.10. Found: N, 6.51; P, 5.19.

Bacterial Alkaline Phosphatase Treatment of 11. 11 (1 mg) was dissolved in Tris-HCl buffer (50 μL, 0.5 M, pH 8.7), and to this solution bacterial alkaline phosphatase (1 μL of a solution of 5 mg of enzyme/mL, 48 units/mg) was added. This solution was incubated overnight at 37 °C. The reaction mixture was split into three parts and chromatographed on Whatman no. 1 paper in solvent systems A, B, and C. The product of this alkaline phosphatase cleavage had R_fs identical to that of authentic 5-nitrouridine (**9**) (R_fs: system A, 0.41; system B, 0.68; system C, 0.63).

Preparation of 5-Nitrouridine 5'-monophosphate (11) by Phosphorylation with $POCl_3$. The method of Yoshikawa et al.[15] was followed. 5-Nitrouridine (**9**, 72.3 mg, 0.25 mmol) was dissolved in a solution of triethyl phosphate (0.63 mL) and phosphoryl chloride (0.05 mL, 0.5 mmol). The mixture was left at room temperature overnight. Ether (25 mL) and water (1 mL) were added, and the resulting mixture was vigorously stirred for 0.5 h in an ice bath. The water phase was separated, neutralized with concentrated NH_4OH, and then applied to Whatman 3MM paper, and the chromatogram developed in solvent system B (descending). Two bands were visualized under UV light. The faster band (R_f 0.74) was determined to be unreacted starting material **9**. The lower band (R_f 0.41) was cut out and extracted with water, and the aqueous solution was evaporated to give a 24% yield of **11**. This product showed a positive periodate–benzidine test and a UV typical of 5-nitrouridine. Hydrolysis of this product with bacterial alkaline phosphatase under conditions described above gave only 5-nitrouridine (R_fs in systems A, B, and C identical to authentic **9**). This product, prepared by phosphorylation of **9**, had identical R_fs to **11**, prepared with NO_2BF_4, in solvent systems A, B, and C and, in addition, cochromatographed with 11 in systems A, B, and C.

Acknowledgments. We express our gratitude to Dr. Harry B. Wood of the National Cancer Institute for an authentic sample of 5-nitrouridine.

Registry No.—**1,** 66-22-8; **3,** 615-77-0; **4,** 28495-88-7; **5,** 874-14-6; **7,** 58-96-8; **9,** 3106-03-4; **10** 2Na, 3387-36-8; **11,** 23568-00-5; **11** Ba, 63689-78-1; **12** 2Na, 42155-08-8; **13,** 63689-79-2; **14** ammonium salt, 63689-80-5; **15,** 3106-01-2; **16,** 63689-81-6; NO_2BF_4, 13826-86-3.

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(20) The ratio of **13** (R_f 0.29) to **14** (R_f 0.54) varied according to the water content of the NO_2BF_4–sulfolane reaction mixture. As determined from the relative heights of the C-6 proton from ^1H NMR, the ratio of *O*-nitrate **14** to **13** was 3:2 when the water content of the reaction was minmized (0.18 equiv mol), 1:1 when 1 molar equiv of H_2O was present, and 2:3 when 2 molar equiv of H_2O was present.

Stereostructures of the Macrocyclic Diterpenoids Ovatodiolide and Isoovatodiolide[1]

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The stereostructures of the 14-membered carbocyclic diterpenoids ovatodiolide (**3**) and isoovatodiolide (**4**), isolated from *Anisomeles indica* (Labiatae), have been established by x-ray crystallographic analyses. Acid treatment of **3** led to facile transannular ring closure to give **5** or **6,** depending on the acid used. The carbobicyclic system present in **5** and **6** occurs in the Gorgonian metabolite eunicellin (**9**).

Since the isolation of the 14-membered macrocyclic diterpene cembrene (**1**), a number of diterpenoids possessing the cembrane ring system (cembrenoids) have been isolated, many of which have shown pronounced biological activities.[2]

Our interest in the cembrenoids stems, in part, from the recognition that **1** and its congener casbene (**2**) are the biogenetic precursors of a variety of transannularly cyclized diterpenoids which exhibit a wide range of biological activities.[3] Prominent among such compounds are the cytotoxic principles of the Euphorbiaceae.[4] Also of some interest, is the in vitro transannular cyclization that the cembrenoids are expected to undergo. Somewhat surprisingly, there is a dearth of information on such cyclizations. In this paper we describe the stereostructures of the crystalline cembrenoids ovatodi-

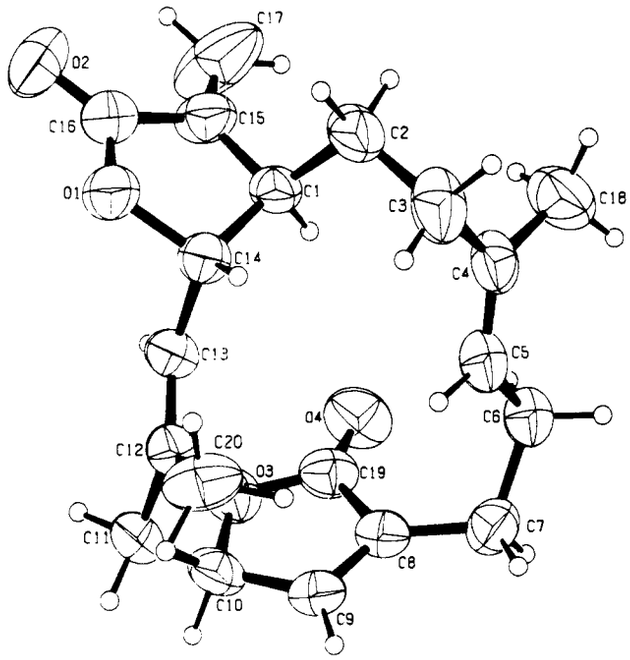
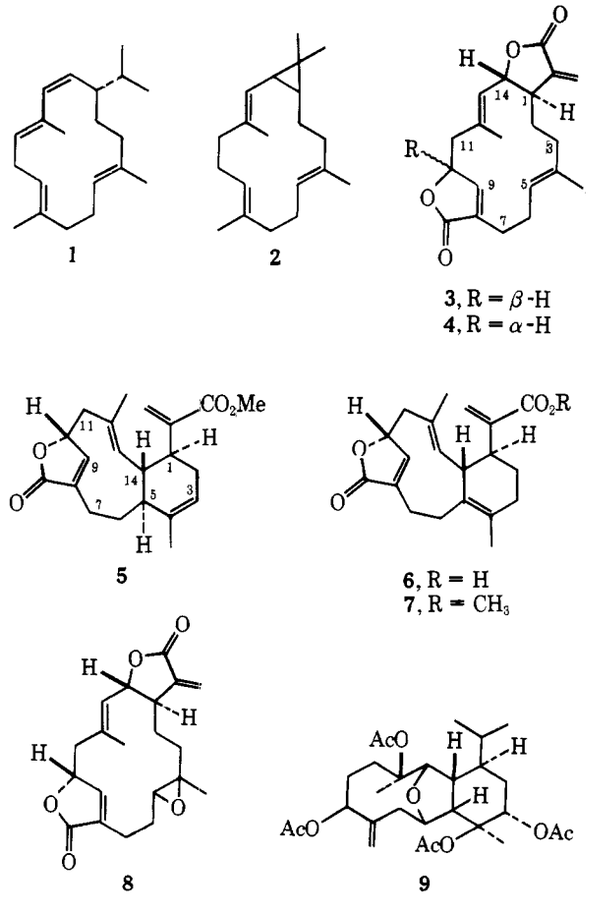


Figure 1. A perspective drawing of **3.**

olide (**3**) and isoovatodiolide (**4**), and the acid-catalyzed conversion of **3** into the bicyclic derivatives **5** and **6.**

Extraction of the leaves of *Anisomeles indica* (Labiatae), a plant occassionally used for stomach ailments in Trinidad,[5] afforded ovatodiolide (**3**) in ~0.2% yield. Ovatodiolide was first isolated[6] from the South Vietnamese plant *A. ovata* by Toubiana and his collaborators. The material isolated by us had physical and chemical properties in complete accord with those reported by Toubiana et al. Based on spectral and



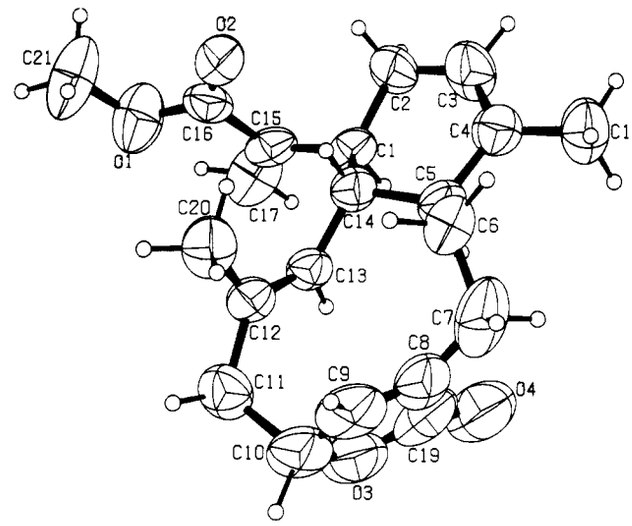


Figure 2. A perspective drawing of **5.**

chemical studies, Toubiana[7] subsequently proposed a gross structure, but without stereochemical assignments, for ovatodiolide. From x-ray crystallographic analysis we have now confirmed the gross structure proposed by Toubiana, and have defined completely the relative stereochemistry of ovatodiolide as depicted in **3.** The solid-state conformation of ovatodiolide is shown in Figure 1. As can be seen from this figure, ovatodiolide is a $\Delta^{5(6)}$-trans,$\Delta^{9(10)}$-trans,$\Delta^{13(14)}$-trans triene dilactone in which the α-methylene lactone is trans fused to the macrocyclic portion of the molecule.

With the structure and stereochemistry of **3** firmly established, we proceeded to examine its behavior under acidic conditions, conditions which we were hoping would effect intramolecular cyclization of the macrocyclic system. When treated with hot methanolic hydrochloric acid, ovatodiolide gave a mixture from which the major component **5** (~40%) was obtained as colorless crystals, mp 185–187 °C, $C_{21}H_{26}O_4$, whose IR spectrum indicated the presence of γ-lactone (1790 cm^{-1}) and ester (1720 cm^{-1}) functionalities. The ^1H NMR spectrum showed that the ester was a methyl ester (δ 3.70) and, in addition, revealed a one-proton multiplet at δ 5.20 which is ascribed to the proton at C-10; in ovatodiolide there were two protons of the H–C–O type. A broad doublet at δ 4.76 (J = 10 Hz) was readily discernible in the product **5,** and is attributed to the olefinic proton at C-13; in **3** absorption due to this proton is obscured by other signals in the δ 4.66–5.30 region. Other absorptions in the NMR spectrum of **5** were similar to those present in **3.** Thus, there were absorptions at δ 1.53 and 1.73 due to the methyl groups C-18 and C-20, respectively, doublets at δ 5.50 (1 H) and 6.26 (1 H) due to the protons on C-17, and a broad singlet at δ 6.88 due to the proton on C-9. Absorption due to H-3 appeared as a multiplet at ca. δ 5.30. From the spectral data we inferred that the α-methylene methyl ester in **5** was formed at the expense of the α-methylene lactone group originally present in **3,** and since the product had the same level of unsaturation and the same number of olefinic protons as in **3,** we concluded that a new carbocyclic system was generated in the reaction of **3** with methanolic HCl. The structure and stereochemistry of the product **5** were eventually solved by x-ray crystallography. A perspective drawing of **5** is given in Figure 2. As can be seen from the figure, a new carbon–carbon bond is formed between C-5 and C-14 to give a cyclohexenyl ring, which is trans fused to a ten-membered ring.

With *p*-toluenesulfonic acid in boiling benzene, ovatodiolide gave a crystalline acid **6,** mp 228–231 °C, $C_{20}H_{24}O_4$. As in the case of **5,** the spectral properties of the acid indicated that the

Table I. Crystal Data and Experimental Details

Compd	3[a]	4[a]	5[a]	6[a]
Space group	$P2_12_12_1$	$P2_1$	$P2_12_12_1$	$P2_12_12_1$
a, Å	10.823 (2)	9.292 (2)	8.22 (1)	9.407 (1)
b, Å	12.915 (3)	11.575 (4)	9.76 (1)	13.048 (2)
c, Å	13.190 (3)	8.896 (2)	23.08 (2)	14.389 (2)
β, deg		102.63 (2)		
Z	4	2	4	4
d_{calcd}, g cm^{-3}	1.183	1.168	1.228	1.234
μ(Cu Kα), cm^{-1}	6.7	6.6	6.8	7.0
Crystal size, mm	0.3 × 0.3 × 0.5	0.15 × 0.3 × 0.9	0.20 × 0.25 × 0.5	0.07 × 0.15 × 0.4
Maximum 0, deg	70	76	57	57
No. of reflections	1975	1966	1465	1392
No. of obsd reflections	1628	1861	1148	1139
Absorption correction	None	None	None	None
Least-squares refinement	Full matrix	Full matrix	Full matrix	Full matrix
Heavier atoms	Anisotropic	Anisotropic	Anisotropic	Anisotropic
Hydrogen atoms	Iso (fixed)	Iso (fixed)	Iso (fixed)	Iso (fixed)
Final R	0.047	0.063	0.077	0.047
Final wR	0.052	0.070	0.082	0.049
Final difference map—largest peak (e Å^{-3})	±0.2	<±0.4	<±0.2	<±0.2

[a] Registry no.: **3**, 3484-37-5; **4**, 63700-26-5; **5**, 63626-07-3; **6**, 63626-08-4.

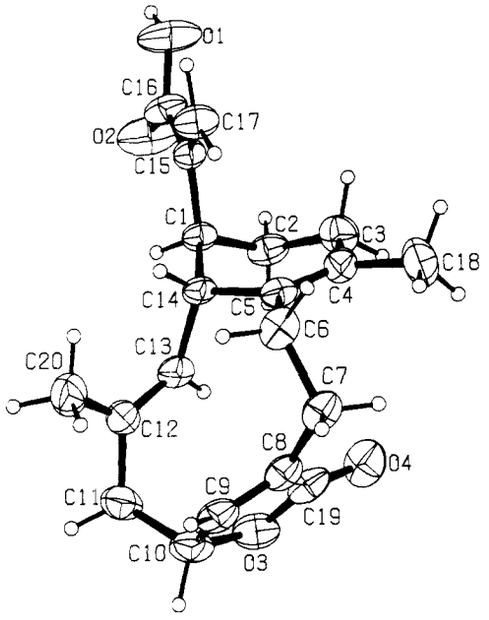


Figure 3. A perspective drawing of **6**.

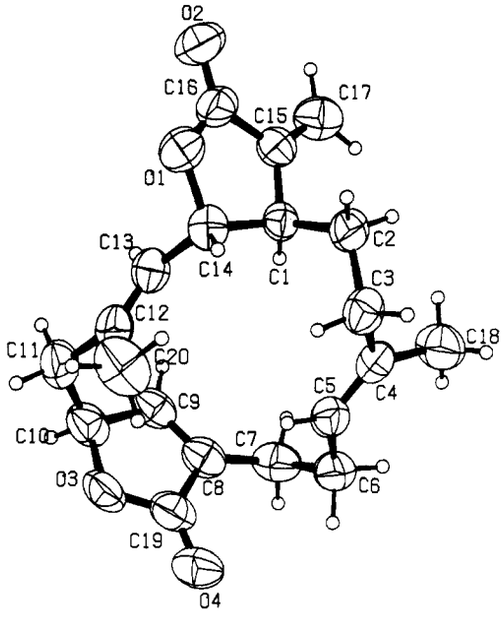


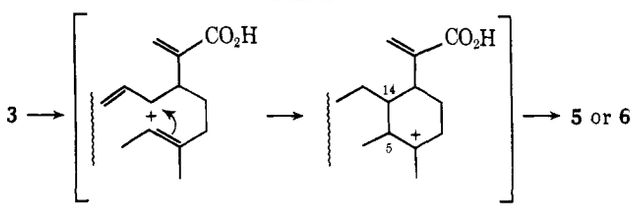
Figure 4. A perspective drawing of **4**.

α-methylene lactone was lost, but unlike **5**, NMR absorption due to the olefinic proton at C-3 was absent. Furthermore, treatment of the acid with methanolic HCl gave a crystalline ester **7**, $C_{21}H_{26}O_4$, whose ^{1}H NMR spectrum was similar to that of **5**, except for the absence of absorption at δ 5.30 (H-3 in **5**). From the spectral evidence we concluded that **7** was isomeric with **5**. This was confirmed by x-ray crystallographic analysis of the acid **6**, a perspective drawing of which is shown in Figure 3.

In a related series of experiments, epoxyovatodiolide (**8**) was treated with a number of acids, and also with molybdenum hexacarbonyl,[8] but in all cases complex mixtures were produced from which we were unable to isolate pure samples.

The formation of **5** and **6** is envisaged to occur via a common allylic carbonium ion, with carbon–carbon bond formation occurring between C-5 and C-14, followed by proton loss from either C-3 or C-5 (see Scheme I). Interestingly, the skeletal system present in **5** and **6** is also present in the Gorgonian metabolite eunicellin (**9**),[9] except that in the latter the carbobicyclic rings are cis fused.

Scheme I



Examination of the mother liquors obtained from the crystallization of ovatodiolide (**3**) led to the isolation of another crystalline diterpenoid, isoovatodiolide (**4**), whose spectral and analytical properties suggested that it was isomeric with ovatodiolide. An x-ray crystallographic analysis of isoovatodiolide revealed the structure and relative stereochemistry shown in **4** and in Figure 4. In **4** the hydrogen at C-10 has the α configuration, whereas in **3** it is β. The absolute stereochemistry of these compounds has yet to be determined.[10]

Crystallography. The crystal data for **3, 4, 5,** and **6,** and the experimental details are summarized in Table I. The intensity data for all four compounds were measured on Hilger–Watts diffractometers (Ni filtered Cu Kα radiation, θ–2θ scans, pulse height discrimination) and the structures were solved by a multiple solution procedure.[11] A fully suitable crystal of **5** was not found; this is reflected in the lower precision for the lattice constants and the higher R values. The estimated standard deviations in the bond lengths and the bond angles in **5** are two to three times those for **3** and **6.** Nevertheless, the analysis was sufficient to define fully the structure and relative stereochemistry of **5.**

Experimental Section

General. Melting points were determined in capillaries on a Thomas–Hoover melting point apparatus and are uncorrected. Unless otherwise indicated, infrared (IR) and nuclear magnetic resonance spectra (NMR) were determined in $CHCl_3$ and $CDCl_3$, respectively. ^1H and ^{13}C NMR spectra were recorded at 60 and 25.4 MHz, respectively. Chemical shifts are expressed in parts per million with tetramethylsilane as internal standard and coupling constants (J) in hertz (s = singlet, d = doublet, t = triplet, m = multiplet). Mass spectra (MS) were determined using a direct inlet system with ionization energy of 70 eV; m/e values are given with relative intensities (%) in parentheses. Thin layer chromatograms (TLC) were made from Merck (Darmstadt) silica gel G; spots were made visible by spraying with 10% phosphomolybdic acid in ethanol and heating the plates to 110 °C.

Isolation of Ovatodiolide (3). Finely-ground, dried leaves (1.5 kg) of *Anisomeles ovata* (Labiatae) collected in Trinidad (Aug 1976) were steeped in 5.0 L of acetone at room temperature for 4 days. The mixture was filtered and the filtrate was evaporated to give 21.2 g of a green gum, a portion (7.0 g) of which was chromatographed on 200 g of neutral alumina (Woelm Grade II, dry pack) with ethyl acetate in hexane (1:1) as eluent. Fractions containing **3** (ascertained by TLC using 65% ethyl acetate in hexane as eluent) were combined and crystallized from 40% ethyl acetate in hexane to give 1.75 g of ovatodiolide (**3**) as colorless prisms: mp 150–151 °C; $[\alpha]^{25}_D$ +22.3° (*c* 1.0, $CHCl_3$); IR 1755, 1660, 1265, 1120 cm^{-1}; Raman (neat) 1760, 1750, 1675, 1655 cm^{-1}; ^1H NMR δ 1.61 (3 H, s, H-18), 1.70 (3 H, d, J = 1 Hz, H-20), 2.90 (1 H, d of d, J = 14 and 4 Hz, H_B-11), 4.66–5.30 (4 H, m), 5.64 (1 H, d, J = 1 Hz, H_A-17), 6.26 (1 H, d, J = 1 Hz, H_B-17), 7.01 (1 H, s, H-9); ^{13}C NMR 15.0 (q, C-18), 19.2 (q, C-20), 23.7 (t, C-2), 24.7 (t, C-3), 33.2 (t, C-6), 36.1 (t, C-7), 40.0 (t, C-11), 42.6 (d, C-1), 77.8 (d, C-10), 78.7 (d, C-14), 122.2 (t, C-17), 124.8 (d, C-5), 128.6 (d, C-13), 131.3 (s, C-4), 133.9 (s, C-12), 134.0 (s, C-15), 139.7 (s, C-8), 147.5 (d, C-9), 169.9 (s, C-19), 172.8 (s, C-16) ppm; ^{13}C NMR assignments are tentative, and are based on chemical shifts and off-resonance decoupled spectra; MS m/e 328 (M^+, 100).

Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.15; H, 7.37. Found: C, 73.33; H, 7.31.

Isolation of Isoovatodiolide (4). TLC (60% ethyl acetate in hexane) examination of the mother liquor obtained from the crystallization of ovatodiolide (**3**) revealed the presence of two major compounds: ovatodiolide (R_f 0.40) and isoovatodiolide (R_f 0.50). Purification of 1.0 g of the mother liquor by preparative-scale TLC (silica gel, 60% ethyl acetate in hexane, short-wavelength UV light) gave 193 mg of isoovatodiolide (**4**) as colorless prisms from ethyl acetate in hexane (1:10): mp 127–128 °C; $[\alpha]^{25}_D$ −316° ($CHCl_3$, *c* 1.0); IR 1775, 1660, 1260, 1120, 970, 940 cm^{-1}; Raman (neat) 1775, 1765, 1680 cm^{-1}; ^1H NMR δ 1.63 (3 H, s, H-18), 1.73 (3 H, d, J = 1 Hz, H-20), 4.70–5.30 (4 H, m), 5.60 (1 H, d, J = 1 Hz, H_A-17), 6.23 (1 H, d, J = 1 Hz, H_B-17), 6.93 (1 H, s, H-9); MS m/e 328 (M^+ 10).

Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.15; H, 7.37. Found: C, 73.20; H, 7.59.

4,5-Epoxyovatodiolide (8). A solution of 328 mg (1.0 mmol) of **3** in 15 mL of methylene chloride was treated with 300 mg of *m*-chloroperbenzoic acid (82%). The mixture was stirred at room temperature for 3 h, diluted with 50 mL of methylene chloride, washed successively with 50 mL of water, 50 mL of saturated $NaHCO_3$, then with 50 mL of saturated brine, and dried ($MgSO_4$). Evaporation of the solvent gave 311 mg of a gum which was purified by chromatography on 30 g of neutral alumina (Grade II, dry pack) with 80% ethyl acetate in hexane as eluent. Removal of the solvents gave 218 mg of a gum which solidified on the addition of 1 mL of ether in hexane (1:1): mp 131–139 °C; $[\alpha]^{25}_D$ −28.6° (*c* 1.0, $CHCl_3$); IR 1770, 1670 cm^{-1}; Raman (neat) 1775, 1680 cm^{-1}; ^1H NMR δ 1.25 (3 H, s, H-18), 1.70 (3 H, d, J = 1 Hz, H-20), 2.95 (1 H, d of d, J = 14 and 2 Hz, H-5), 4.82 (1 H, d of d, J = 10 and 2 Hz, H-14), 5.14 (1 H, br s, H-13), 5.21 (1 H, m, H-10), 5.64 (1 H, d, J = 2 Hz, H_A-17), 6.20 (1 H, d, J = 2 Hz, H_B-17), 7.16 (1 H, s, H-9); ^{13}C NMR 16.2 (q, C-18), 19.6 (q, C-20), 23.1 (t, C-2), 24.8 (t, C-6), 31.3 (t, C-3), 35.3 (t, C-7), 39.5 (t, C-11), 43.7 (d, C-1), 58.2 (s, C-4), 60.3 (d, C-5), 77.6 (d, C-10), 79.2 (d, C-14), 122.8 (t, C-17), 127.9 (d, C-13), 132.4 (s, C-12), 133.4 (s, C-15), 138.8 (s, C-8), 147.7 (d, C-9), 169.4 (s, C-19), 172.5 (s, C-16) ppm; MS m/e 344 (M^+, 5).

Anal. Calcd for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02. Found: C, 69.50; H, 7.14.

Treatment of Ovatodiolide (3) with Methanolic Hydrochloric Acid: Compound 5. A solution of 328 mg (1.0 mmol) of ovatodiolide (**3**) in 10 mL of methanol was treated with 3.0 mL of concentrated hydrochloric acid, and the mixture was boiled under reflux for 3.25 h. The mixture was cooled to room temperature, diluted with 50 mL of water, and extracted with 70 mL of ethyl acetate. The extract was washed with saturated brine (until neutral), dried ($MgSO_4$), and evaporated to give 316 mg of a gum whose TLC (50% ethyl acetate in hexane) revealed the presence of four compounds (R_f 0.60, 0.50, 0.41, and 0.20). The compound having R_f 0.50 was isolated (201 mg) by preparative-scale TLC (50% ethyl acetate in hexane, short-wavelength UV light) and crystallized repeatedly from methanol (0 °C, 18 h) to give 103 mg of **5:** mp 185–187 °C; $[\alpha]^{25}_D$ +81° (*c* 1.0, $CHCl_3$); IR 1745, 1715 cm^{-1}; Raman (neat) 1760, 1720, 1660, 1650, 1640 cm^{-1}; ^1H NMR δ 1.53 (3 H, d, J = 1 Hz, H-18), 1.73 (3 H, s, H-20), 3.70 (3 H, s, $COOCH_3$), 4.76 (1 H, br d, J = 10 Hz, H-13), 5.20 (1 H, m, H-10), 5.30 (1 H, m, H-3), 5.43 (1 H, d, J = 1 Hz, H_A-17), 6.06 (1 H, d, J = 1 Hz, H_B-17), 6.88 (1 H, s, H-9); MS m/e 342 (M^+ 16). Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.66, H, 7.65. Found: C, 73.38; H, 7.80.

Treatment of Ovatodiolide (3) with *p*-Toluenesulfonic Acid: Compound 6. A solution of 328 mg (1.0 mmol) of **3** in 10.0 mL of benzene was treated with 190 mg of *p*-toluenesulfonic acid, and the mixture was boiled under reflux for 1.75 h. The solvent was evaporated, and 50 mL of CH_2Cl_2 was added to the residue, followed by 50 mL of 1.0 N NaOH. The organic phase was discarded and the aqueous phase was acidified with cold (5 °C) 1.0 N HCl. The mixture was extracted with CH_2Cl_2 (2 × 50 mL), washed with saturated brine (70 mL), dried ($MgSO_4$), and evaporated to give a semisolid which gave **6** as colorless prisms (193 mg) from methanol (0 °C overnight): mp 228–231 °C; $[\alpha]^{25}_D$ −60.2° (*c* 1, CH_3OH); IR 3160, 1760, 1700, 1650 cm^{-1}; Raman (neat) 1740, 1725, 1675, 1650 cm^{-1}; ^1H NMR δ 1.60 (3 H, d, J = 1 Hz, H-18), 1.75 (3 H, s, H-20), 4.90 (1 H, d, J = 10 Hz, H-13), 5.22 (1 H, m, H-10), 5.42 (1 H, d, J = 1 Hz, H_A-17), 6.20 (1 H, d, J = 1 Hz, H_B-17), 6.80 (1 H, s, H-9); MS m/e 328 (M^+, 46).

Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.15; H, 7.37. Found: C, 73.08; H, 7.22.

Ester 7. A solution of 65.6 mg (0.2 mmol) of **5** in 3.0 mL of methanol was treated with 0.5 mL of concentrated HCl. The mixture was boiled under reflux for 3 h, cooled to room temperature, and worked up as described for **5.** A gum was obtained which was purified by preparative-scale TLC (1:1 ethyl acetate–hexane) to give a solid. Crystallization from methanol (0 °C, 6 h) afforded 44 mg of **7:** mp 141–143 °C; $[\alpha]^{25}_D$ −75.6° (*c* 1, $CHCl_3$); IR 1755, 1720 cm^{-1}; Raman (neat) 1765, 1730, 1670, 1660, 1645 cm^{-1}; ^1H NMR δ 1.56 (3 H, d, J = 1 Hz, H-18), 1.73 (3 H, s, H-20), 3.75 (3 H, $COOCH_3$), 4.92 (1 H, d, J = 11 Hz, H-13), 5.23 (1 H, m, H-10), 5.43 (1 H, d, J = 1 Hz, H_A-17), 6.13 (1 H, d, J = 1 Hz, H_B-17), 6.83 (1 H, s, H-9); MS m/e 342 (M^+, 20).

Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65. Found: C, 73.76; H, 7.63.

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Registry No.—**7,** 62854-00-6; **8,** 4795-48-6.

Supplementary Material Available: Listings of final atomic and anisotropic parameters are given in Tables II and III for **3,** Tables IV and V for **5,** Tables VI and VII for **6,** and Tables VIII and IX for **4** (8 pages). Ordering information is given on any current masthead page.

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Transfer of Chirality in the [2,3] Sigmatropic Rearrangement of Allylic Alcohols to β,γ-Unsaturated Amides. Preparation of Optically Active Nine- and Fourteen-Carbon Saturated Isoprenoid Synthons

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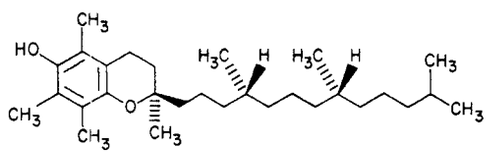
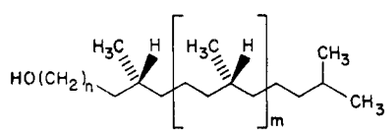
Reaction of optically active (*R,Z*)-allylic alcohols **8** and **16**, respectively, with *N,N*-dimethylformamide dimethyl acetal proceeded stereoselectively, via a [2,3] sigmatropic rearrangement, to give optically active (2*R,E*)-β,γ-unsaturated amides **9** and **17**, with nearly 100% chiral transmission. The (*S,E*)-allylic alcohols **13** and **21**, however, afforded mixtures of (2*R,E*)- and (2*S,Z*)-β,γ-unsaturated amides, from which the nearly optically pure (2*R,E*) isomer could be isolated by chromatography. The optically active amides **9** and **17** were transformed, respectively, into 2(*R*),6-dimethylheptan-1-ol (**2**) and 2(*R*),6(*R*),10-trimethylundecan-1-ol (**4**), which are important intermediates in vitamin E synthesis.

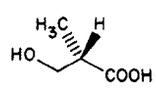
The optically active aliphatic side-chain synthons **2**–**5** are important intermediates in the synthesis of (2*R*,4′*R*,8′-*R*)-α-tocopherol[1] (**1**, vitamin E). The 14- and 15-carbon units **4**[2] and **5**,[3] respectively, were first prepared by degradation of natural phytol. Recently, the preparation of optically active synthons **2** (9-carbon unit) and **4** (14-carbon unit) from (*S*)-(+)-β-hydroxyisobutyric acid (**6**) was reported.[4] Since the homologous units **3** and **5** had been synthesized starting from isovaleraldehyde (**7**) via stereoselective Claisen rearrangements[5] of optically active allylic alcohols, we were also interested in the possibility of preparing the lower homologues **2** and **4** from **7**, using a related approach involving [2,3] sigmatropic shifts.



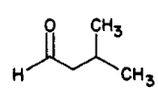
1



	m	n
2	0	0
3	0	1
4	1	0
5	1	1



6



7

The transmission of chirality in a [2,3] sigmatropic process was observed in the conversion of sulfenates to sulfoxides,[6] and later in the Wittig[7] and allylic amine oxide[8] rearrangements. Although the conversion of an allylic halide to a carboxylic acid via a [2,3] sigmatropic process had been recorded,[9] the transmission of chirality associated with a new carbon–carbon bond formation by such a process was noted only in the Wittig rearrangement.[7] Büchi and co-workers[10] recently discovered that allylic alcohols could be transformed into homologous β,γ-unsaturated amides via a [2,3] sigmatropic process, by heating with *N,N*-dimethylformamide acetals. These findings, together with our earlier observations[5] that several variants of the Claisen rearrangement proceeded with essentially 100% chiral transmission, led to the expectation that optically active allylic alcohols should give enantiomerically enriched β,γ-unsaturated amides by the Büchi process. In this report, we wish to present the results of a thorough investigation into the extent of chiral transmission in this one carbon homologation process. The application of this [2,3] sigmatropic rearrangement to the synthesis of optically active saturated isoprenoid synthons **2** and **4** will also be described.

Results

Reaction of the (*R,Z*)-allylic alcohol **8** (96.5% *R*, 3.5% *S*; prepared from isovaleraldehyde as reported earlier[5]) with *N,N*-dimethylformamide dimethyl acetal[10] in refluxing xylene for 93 h gave, in 49% yield, the optically active β,γ-unsaturated amide **9**. (Scheme I). ^{1}H NMR studies on this compound using tris(3-(heptafluoropropylhydroxymethyl)-*d*-camphorato)-europium(III) [Eu(hfc)$_3$] revealed the presence of two pairs