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Odoriferous C_{11} Hydrocarbons from Hawaiian *Dictyopteris*

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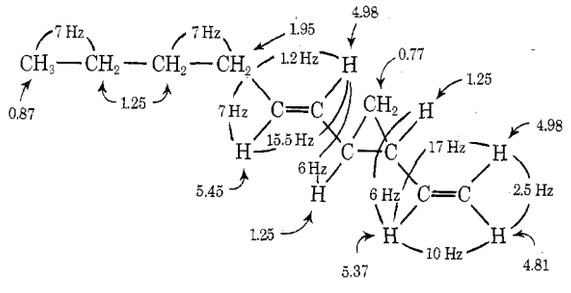
Dictyopterene A [(+)-(*R,R*)-*trans*-1-(*trans*-hex-1′-enyl)-2-vinylcyclopropane], dictyopterene B [(−)-(*R,R*)-*trans*-1-(*trans,cis*-hexa-1′,3′-dienyl)-2-vinylcyclopropane], and dictyopterene C′ [(−)-(R)-6-butycyclohepta-1,4-diene] are the major constituents of the essential oils of the brown Hawaiian seaweeds *Dictyopteris plagiogramma* (Montagne) Vickers and *D. australis* Sonder. Dictyopterene D′ [(+)-(*S*)-6-(*cis*-but-1′-enyl)cyclohepta-1,4-diene], the trans,cis, trans,trans, and cis,trans isomers of 1,3,5-undecatriene, *trans,trans,trans*-2,4,6-undecatriene, *trans,cis,cis*-1,3,5,8-undecatetraene, and *trans,trans,cis*-1,3,5,8-undecatetraene are minor components of the essential oils of Hawaiian *Dictyopteris*.

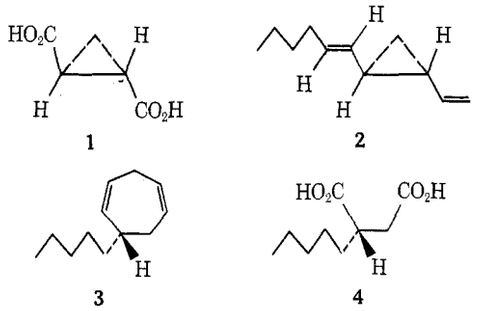
The odoriferous seaweeds *Dictyopteris plagiogramma* (Montagne) Vickers and *D. australis* Sonder grow abundantly on the shores of the Hawaiian Islands. The essential oils of both species of Hawaiian *Dictyopteris* consist of several identical C_{11} hydrocarbons which can be separated by chromatography.

Dictyopterene A. About 25% of the essential oil is dictyopterene A, an optically active oil which was isolated by gas chromatography of the essential oil or fraction 1 from chromatography of the essential oil on silica impregnated with silver nitrate. A molecular weight of 150 was indicated by mass spectrometry which corresponded to the molecular formula $C_{11}H_{18}$. The 100-MHz proton nmr spectrum, shown in Figure 1a, appeared rather complex but with the aid of double-resonance experiments, could be simplified and completely analyzed and was consistent with a *trans*-1,2-cyclopropane possessing vinyl and *trans*-1-hexenyl substituents.[1,2]

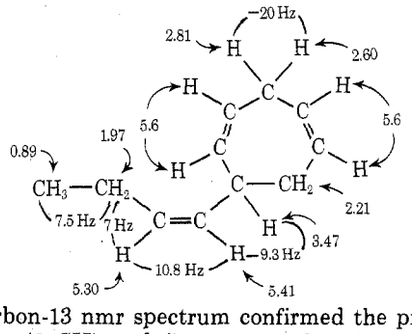


Dictyopterene A had an ultraviolet spectrum similar to that of vinylcyclopropane and its carbon-13 nmr spectrum confirmed the presence of four olefinic (3 CH and 1 CH_2) and seven saturated carbons (2 CH, 4 CH_2, and 1 CH_3). Lemieux oxidation[3] or ozonolysis of dictyterene A afforded formic acid, *n*-valeric acid, and (+)-(*S,S*)-*trans*-cyclopropane-1,2-dicarboxylic acid[4] (1). Isolation of 1 secured the proposed structure and established configuration of dictyopterene A as (+)-(*R,R*)-*trans*-1-(*trans*-hex-1′-enyl)-2-vinylcyclopropane (2).[5]

Dictyopterene A rearranged above 140° to (+)-(*S*)-6-butylcyclohepta-1,4-diene (3). The absolute configuration of C-6 in 3 was deduced to be *S* as ozonolysis of 3 led to malonic acid and the known (−)-(*S*)-butylsuccinic acid (4).[6]



Dictyopterene B. The major component of the essential oil (50%) was first isolated by preparative gas chromatography as a levorotatory oil showing only end absorption in its ultraviolet spectrum and having a molecular weight of 148 by mass spectrometry ($C_{11}H_{16}$). Analysis of the 100-MHz proton nmr proton was consistent with the following structure.[7]



The carbon-13 nmr spectrum confirmed the presence of six olefinic (6 CH) and five saturated carbons (1 CH, 3 CH_2, 1 CH_3). Ozonolysis of this compound yielded malonic and propionic acids but most importantly partial reduction with diimide gave 3, thus establishing its structure as (−)-(*R*)-6-(*cis*-but-1′-enyl)cyclohepta-1,4-diene (5). The cis geometry of the C=C bond in the butenyl

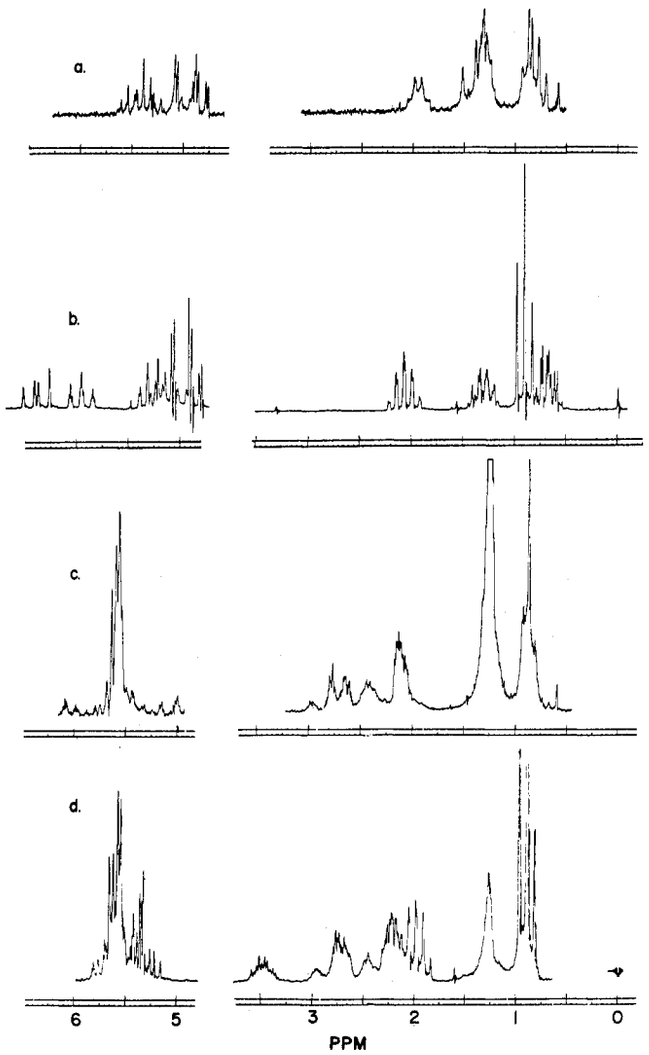
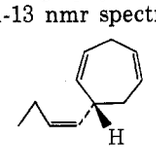


Figure 1. The 100-MHz proton nmr spectra of (a) dictyopterene A in $CDCl_3$, (b) dictyopterene B in benzene-d_6, (c) dictyopterene C′ or **3** in benzene-d_6, and (d) dictyopterene D′ or **5** in benzene-d_6. In d the broad peak at δ 1.25 is an impurity.

side chain was supported by the carbon-13 chemical shifts for the C-3′ methylene (δ 21.0) and C-6 methine (δ 36.5) carbons;[8] these carbons are apparently shielded owing to a van der Waals interaction between the methylene and methine protons.[9]

We immediately suspected that **5** was an artifact produced from gas chromatography of the essential oil. Comparison of the carbon-13 nmr spectrum of **5** with that of



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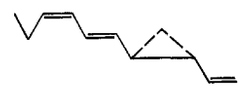
the essential oil (Figure 2) revealed that **5** was not the major constituent of the essential oil. Furthermore, gas chromatography of the essential oil at a lower temperature showed that **5** was being formed on the column by isomerization of another substance with a longer retention time.

The major constituent of the essential oil, dictyopterene B, should therefore have structure **6** and **5** be the result of its Cope rearrangement on the column. The carbon-13 data (Figure 2) were in agreement with structure **6** as the major constituent of the essential oil, showing the presence of six olefinic and five saturated carbons. To preserve



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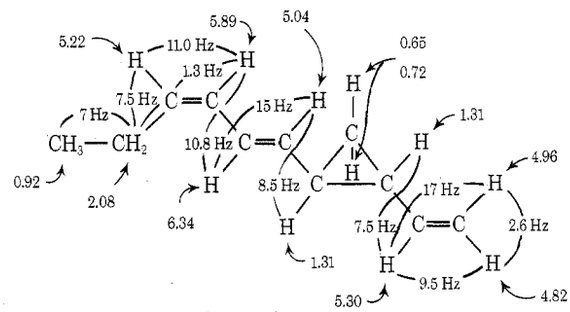
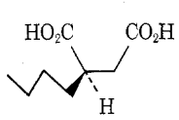
the integrity of this compound during the isolation we resorted to column chromatography on silver nitrate–silica gel, and dictyopterene B was obtained as a levorotatory oil showing ultraviolet absorption at 247 nm. Analysis of the 100-MHz proton nmr spectrum of dictyopterene B (Figure 1b) confirmed structure **6**.[7]



As expected the cis C-2 and C-5 carbons of the *trans,cis*-1,3-hexadienyl group experience van der Waals shielding[9] and were found to resonate at δ 124.2 and 21.28, respectively, in the carbon-13 nmr spectrum. Lemieux oxidation or ozonolysis of dictyopterene B yielded formic acid, propionic acid, and **1**. On the basis of these data we concluded that dictyopterene B is (−)-(*R,R*)-*trans*-1-(*trans,cis*-hexa-1′,3′-dienyl)-2-vinylcyclopropane (**6**).[10]

Dictyopterene C′. Comparison of the carbon-13 nmr spectra of **3** and the essential oil (Figure 2) suggested that the essential oil contained a constituent with the gross structure of **3**. Indeed gas chromatography of the essential oil indicated the presence of a component (10%) with the same retention time as **3**. This new material, dictyopterene C′, was obtained after column and gas chromatography of the essential oil. The proton nmr spectrum of dictyopterene C′ (Figure 1c) was found to be identical with that of **3**, but dictyopterene C′ differed from **3** in sign of optical rotation (negative) and in optical purity and yielded (+)-(*R*)-butylsuccinic acid (**7**) on oxidation. Dictyopterene C′ therefore is (−)-(*R*)-6-butylcyclohepta-1,4-diene (**8**).[11]



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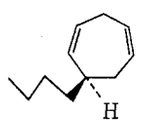

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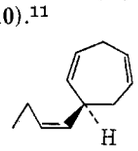
Dictyopterene D′. Carbon-13 nmr analysis suggested that a compound which is enantiomeric with **5** was present in the essential oil (Figure 2). This new compound, dictyopterene D′, was isolated only after tedious column chromatography on silver nitrate–silica gel followed by preparative gas chromatogrphy. The optically active oil had a retention time on the gas chromatograph and a nmr spectrum (Figure 1d) identical with those of **5**, but as suspected its optical rotation was opposite in sign (positive). Dictyopterene D′ is therefore (+)-(*S*)-6-(*cis*-but-1′-enyl)-cyclohepta-1,4-diene (**10**).[11]



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Dictyopterene D′ was identical in all respects, including optical properties, with the male-attracting substance, ec-

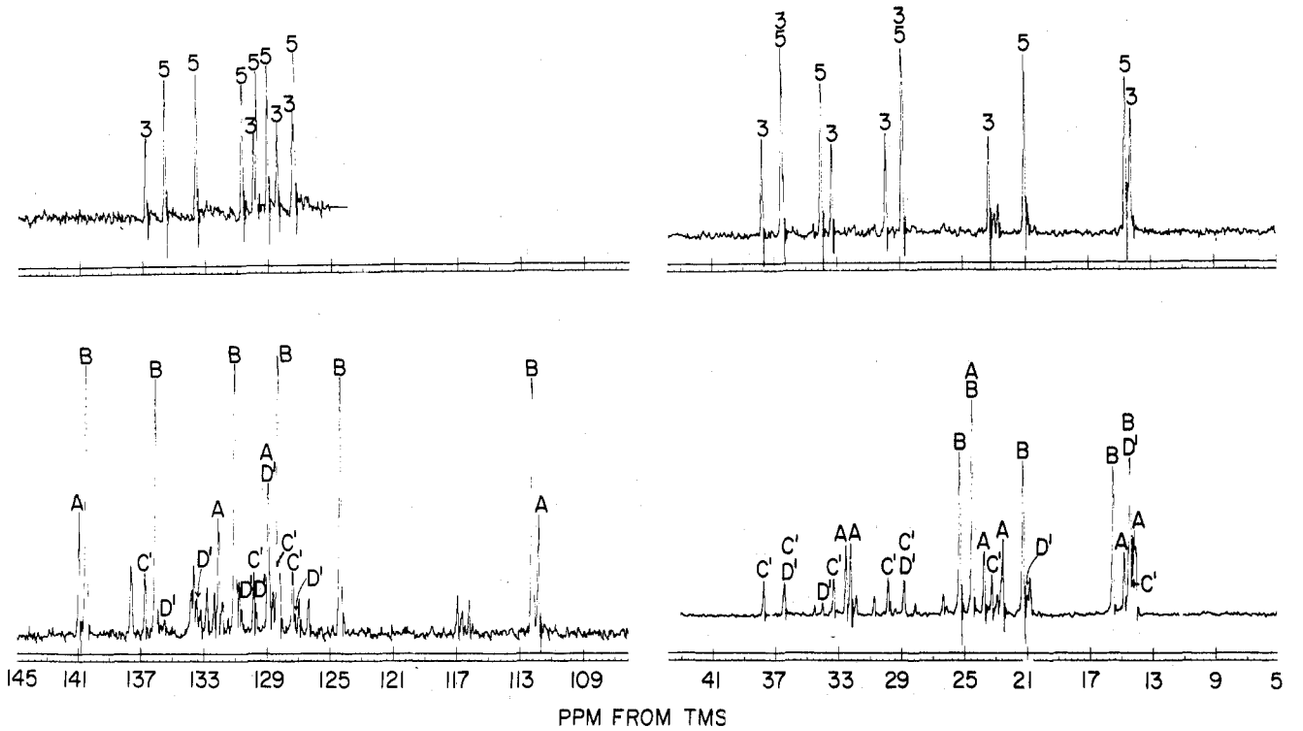
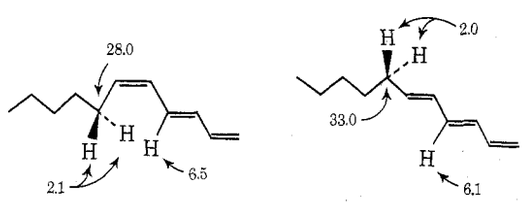


Figure 2. Proton noise decoupled carbon-13 nmr spectra of the essential oil of Hawaiian *Dictyopteris* (lower traces) and a mixture of 3 and 5 (upper traces); 0.5 ml of essential oil/0.5 ml of dioxane, 0.7 ml of mixture of 3 and 5/0.7 ml of dioxane, 8-mm tube, 584 and 1161 scans of low- and high-field regions for the essential oil, 100 and 419 scans of low- and high-field regions for mixture of 3 and 5.

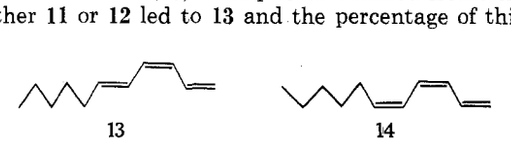
tocarpene, excreted by the female gametes of the brown alga *Ectocarpus siliculosus*.[12,13]

Undecatrienes. About 3% of the essential oil was a 2:1 mixture of the known compounds *trans,cis*-1,3,5-undecatriene (**11**) and *trans,trans*-1,3,5-undecatriene (**12**).[14] This



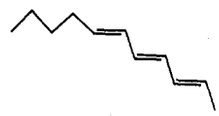
mixture of trienes was obtained by chromatography of the essential oil on silver nitrate–silica gel and further separation was only achieved by gas chromatography. We found that **11** and **12** could be readily distinguished by comparing the proton and carbon-13 chemical shifts of the two isomers. The van der Waals interaction between the C-4 methine proton and C-7 methylene protons of **11** causes deshielding of the protons (signals appear downfield with respect to those of **12**) and concomitant shielding of the carbons (signals appear upfield with respect to those of **12**).[15]

Detailed analysis of the 1,3,5-undecatriene mixture from *Dictyopteris* by gas chromatography indicated that trace amounts of several other constituents were present; these substances were also found in commercial samples of 1,3,5-undecatriene. One of the components had a gc retention time which was identical with that of *cis,trans*-1,3,5-undecatriene (**13**). The photosensitized isomerization of either **11** or **12** led to **13** and the percentage of this isomer in the photostationary state equilibrium mixture increased inversely with the total triene concentration.[16] When this mixture of trienes was treated with maleic anhydride in refluxing benzene, **11** and **12** formed Diels–Alder adducts but **13** and *cis,cis*-1,3,5-undecatriene (**14**) did not react under these conditions.[17] Only a very small amount of **14** appeared to be present and therefore fairly pure **13** could be obtained by this procedure.



The proton nmr spectrum of **13** exhibited a doublet of triplets at δ 5.67 for the C-6 hydrogen which showed trans coupling (J = 15.6 Hz) to the C-5 proton and vicinal coupling (J = 7.2 Hz) to the C-7 methylene protons. The C-5 olefinic proton resonance was displayed by a doublet of doublets at δ 6.44 and its low field position resulted from van der Waals deshielding by the C-2 proton. Irradiation of a broad quartet at δ 2.08 for the C-7 methylene reduced the C-6 signal to a doublet and removed the fine structure (long-range coupling) from the C-5 signal. The C-2 proton resonated as a doublet (J = 17.1 Hz) of triplets (J = 10.2 Hz) at δ 6.74 and again the low field position of this signal reflected the van der Waals interaction of the C-2 and C-5 protons. The C-2 and C-5 protons of **11** and **12** resonated at higher field, near δ 6. The geometry of the Δ^3 double in **13** had to therefore be cis.

Four 2,4,6-undecatrienes were also found in both the algal and commercial samples of 1,3,5-undecatriene. All four isomers appeared to survive treatment with maleic anhydride in refluxing benzene and had much longer gc retention times than those of the 1,3,5-undecatrienes. Only one isomer, however, could be obtained in sufficient quantity and purity by gas chromatography for complete spectral analysis. This isomer was concluded to be *trans,trans,trans*-2,4,6-undecatriene (**15**), as its infrared spectrum showed a very large absorption at 970 cm^{-1} for trans olefinic bonding, but no absorption indicative of cis disubstitution. The proton nmr spectrum of **15** was also consistent with this assignment, as the olefinic region showed



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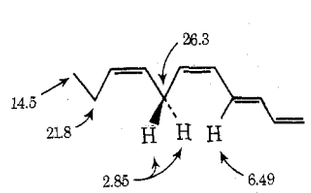
only two broad signals centered at δ 5.5 and 6.0 for the two "outer" and four "inner" trans-type protons, respectively; absorptions at lower field (*ca.* δ 6.5) would have been seen if any double bonds were cis. The spectrum also showed a doublet at δ 1.72 (J = 6.5 Hz) for a methyl group and multiplets at δ 2.04, 1.31, and 0.89 for a *n*-butyl group attached to the ends of the triene chromophore. Irradiation at δ 5.5 reduced the doublet for the C-1 methyl group to a singlet and the broad quartet for the C-8 methylene to a broad triplet.

The other three 2,4,6-undecatrienes are probably Δ^2 and Δ^6 cis isomers.

Undecatetraenes. Two other conjugated trienes were present in the essential oil in equal amounts (3%) from uv evidence. Mass spectral analysis, however, indicated that both hydrocarbons had molecular weights of 148 corresponding to the molecular formula $C_{11}H_{16}$ and hence each compound possessed an additional unconjugated double bond or ring. The proton nmr spectrum of each hydrocarbon showed the familiar triplet and quintet for an ethyl group attached to an olefinic methine, a broad triplet attributed to a methylene group flanked by two olefinic methines, and two doublets of doublets in the high-field olefinic region reminiscent of a vinyl group. Complete analysis showed that the hydrocarbon from fraction 4 (silver nitrate–silica gel chromatography) is *trans,cis,cis*-1,3,5,8-undecatetraene (16).[7]

Carbon-13 nmr spectra of the two individual undecatetraenes were not obtained; the spectrum of the mixture, however, was determined and showed some interesting features. First of all the chemical shifts for the ethyl group carbons were identical for the two isomers. Both compounds, therefore, had to have structural similarily in the vicinity of the ethyl group; *i.e.*, like **16** the hydrocarbon from fraction 3 (silver nitrate–silica gel chromatography) had to be a Δ^8 *cis*-1,3,5,8-undecatetraene. Secondly, comparison of the C-4 and C-7 proton and carbon chemical shifts for the two isomers indicated that the Δ^5 double bond of the tetraene from fraction 3 was trans and that its structure was most probably **17**.



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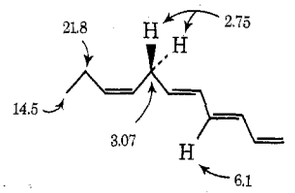

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The Δ^5 and Δ^8 double-bond assignments were affirmed by decoupling experiments. Irradiation at 5.4 ppm reduced the quintet at δ 1.97 (C-10 methylene) to a quartet and the triplet at δ 2.75 (C-7 methylene) to a singlet. Irradiation at δ 1.97 collapsed the multiplet at δ 5.42, assigned to the C-9 proton, to a doublet (J = 11 Hz), thus confirming the cis geometry of the Δ^8 double bond. Irradiation of the C-7 methylene (δ 2.75), on the other hand, reduced the multiplet at δ 5.34, attributed to the C-8 proton, to a doublet (J = 11 Hz) and the doublet of triplets at δ 5.54 (C-6 proton) to a doublet (J = 17 Hz), establishing the Δ^5 double bond as trans. The Δ^3 double bond was concluded to be trans owing to the close similarity of the chemical shifts for the C-3, C-4, and C-5 protons (all *ca.* δ 6.1) and by analogy with **12**. Thus the hydrocarbon from fraction 3 is concluded to be *trans,trans,cis*-1,3,5,8-undecatetraene (17).

Experimental Section[18]

Isolation of the Hydrocarbons. *Dictyopteris plagiogramma* (Montagne) Vickers and *D. australis* Sonder (drift material) were collected at Sandy Beach, near the Halona Blowhole, Oahu. No attempt was made to separate the two seaweeds, which were drifting together in about a 4:1 ratio, respectively. In a typical work-up the freshly collected, wet seaweed (*ca.* 42 lb) was digested three times with 15% methanol–chloroform for 2 days each and the extracts were separated, combined, and evaporated under reduced pressure. The residual oil (70.5 g) was distributed between 1.5 l. of *n*-heptane saturated with methanol and 1.5 l. of methanol saturated with *n*-heptane and each layer was backwashed with 300 ml of solvent. Evaporation of the methanol layer gave 30 g of fraction B. The heptane layer and washings (upper phases) were combined and evaporated and molecular distillation of the oil at 40° (0.25 mm) for 1 day yielded 28 g of essential oil and 12 g of residue (fraction A).

The essential oil (11 g) in *n*-pentane was introduced onto a 4.9 × 74 cm column of 25% silver nitrate–silica gel at 25° and the chromatogram was developed with 2 l. of 1% ether–pentane. Elution with 4 l. of 3% ether–pentane removed 400 mg of oil (fraction 1) followed by 1.7 g of oil (fraction 2). Fraction 1 exhibited ultraviolet absorption at 253, 262, and 273 nm and was essentially a 2:1 mixture of *trans,cis*- and *trans,trans*-1,3,5-undecatriene having retention times of 31 and 33 min, respectively, on a 30 ft × 0.125 in. column of 30% DEGS on Chromosorb W (100/120 mesh; column temperature, 120°; injector temperature, 170°; nitrogen flow rate, 20 ml/min); fraction 2, on the other hand, exhibited ultraviolet absorption at 210 nm and was a 2:1 mixture of dictyopterenes A and C′ having retention times of 21 and 29 min, respectively. Further elution with 2 l. of 5% ether–pentane and 1.2 l. of 10% ether–pentane removed successively 550 mg of colorless oil and 740 mg of pale yellow oil (fraction 5). The forerun exhibited ultraviolet absorption at 254, 263, and 274 nm and was a 1:1 mixture of *trans,cis,cis*- and *trans,trans,cis*-1,3,5,8-undecatetraene having retention times of 44 and 47 min, respectively, on the 30% DEGS column; occasionally the forerun separated on the silica gel–silver nitrate column into the trans,trans,cis (fraction 3) and the trans,cis,cis isomers (fraction 4). Fraction 5 exhibited ultraviolet absorption at 247 nm and was fairly pure dictyopterene B, a compound which isomerized on the 30% DEGS column above and showed a retention time of 35 min for the rearranged dictyopterene B. Elution was continued with 2 l. of 20% ether–pentane, 9 l. of 30% ether–pentane, and 2 l. of 60% ether–pentane, which removed about 7 mg of oil (fraction 6). Fraction 6 exhibited ultraviolet absorption at 281, 294, and 308 nm for a conjugated tetraene, but was a complex mixture that showed the presence of a component, dictyopterene D′, with a retention time (35 min) identical with that of rearranged dictyopterene B on the 30% DEGS column.

Fraction 1 was separated into *trans,cis*-1,3,5-undecatriene (11) and *trans,trans*-1,3,5-undecatriene (12) by preparative gas chromatography on a 20 ft × 0.375 in. column of 25% TCEP on Chromosorb P (column temperature, 115°; injector temperature 125°; nitrogen flow rate, 150 ml/min) in 0.075-ml portions. *trans,cis*-1,3,5-Undecatriene was identical with an authentic sample[14] and had the following properties: uv (*n*-pentane) λ_{max} 244 (sh), 253, 262, 273 nm; proton nmr (benzene-d_6) δ 0.92 (t, 3 H, J = 7.5 Hz), 1.25 (m, 6 H), 2.1 (m, 2 H), 5.01 (dd, 1 H, J = 9 and 2 Hz), 5.14 (dd, 1 H, J = 16 and 2 Hz), 5.43 (dt, 1 H, J = 11 and 7 Hz), 6.0–6.6 (m, 4 H); carbon-13 nmr δ 14.1 (CH_3), 22.9 (CH_2), 28.0 (CH_2), 29.6 (CH_2), 31.7 (CH_2), 116.8 (CH_2), 129.0 (2 CH), 133.5 (2 CH), 137.7 (CH). *trans,trans*-1,3,5-Undecatriene was identical with an authentic sample[14] and had the following properties: uv (*n*-pentane) λ_{max} 244 (sh), 253, 262, 273 nm; carbon-13 nmr δ 14.1 (CH_3), 22.9 (CH_2), 29.3 (CH_2), 31.7 (CH_2), 33.0 (CH_2), 116.1 (CH_2), 130.8 (CH), 131.5 (CH), 134.0 (CH); 136.0 (CH), 137.7 (CH). On a 200 ft × 0.01 in. TCEP capillary column (column temperature, 75°; injector temperature, 100°) fraction 1 showed the presence of trace amounts of 5-*n*-pentylcyclohexa-1,3-diene (tentative), *cis,trans*-1,3,5-undecatriene (13), and four 2,4,6-undecatriene isomers with retention times of 0.58, 1.06, 1.25, 1.28, 1.37, and 1.42, respectively, relative to those of 11 (1.00) and 12 (1.03). The retention times of these trace compounds were identical with those of minor constituents or impurities in an authentic sample of 1,3,5-undecatriene (obtained from International Flavors and Fragrances).

Fraction 2 in 3.5 ml of *n*-pentane was chromatographed preparatively on a 30 ft × 0.375 in. column of 30% DEGS on Chromosorb W (column temperature, 125°; injector temperature, 160°; nitrogen flow rate, 165 ml/min) in 0.35-ml portions to give after molecular distillation[19] 640 mg of **dictyopterene A (2)** and 230 mg of **dictyopterene C′ (8).** Dictyopterene A, a colorless oil, had the following properties: $[\alpha]^{22}D$ +72° ($CHCl_3$, *c* 6.74); $[\theta]_{<185\,nm}$ >+50,000, $[\theta]_{207\,nm}$ −20,000, $[\theta]_{232\,nm}$ +5600; ir (CCl_4) ν_{max} 3080, 3000, 2960, 2920, 2850, 1630, 1450, 1210 cm^{-1}; uv (95% EtOH) λ_{max} 206 nm (ϵ 16,000); proton nmr ($CDCl_3$) δ 0.77 (t, 2 H), 0.89 (t, 3 H, J = 7 Hz), *ca.* 1.25 (m, 6 H), 1.95 (q, 2 H, J = 7 Hz), 4.81 (dd, 1 H, J = 10 and 2.5 Hz), 4.98 (dd, 1 H, J = 17 and 2.5 Hz), 4.98 (ddt, 1 H, J = 15.5, 6, and 1.2 Hz), 5.37 (ddd, 1 H, J = 17, 10, and 6 Hz), 5.45 (dt, 1 H, J = 15.5 and 7 Hz); carbon-13 nmr δ 14.2 (CH_3), 14.8 (CH_2), 22.5 (CH_2), 23.7 (CH), 24.5 (CH), 32.1 (CH_2), 32.5 (CH_2), 111.8 (CH_2), 128.9 (CH), 132.0 (CH), 140.9 (CH); mass spectrum (70 eV) *m/e* (rel intensity) 150 (4), 121 (2), 107 (5), 105 (2), 93 (31), 91 (26), 79 (100), 77 (26), 67 (25), 66 (22), 55 (11), 41 (44), 39 (20), 29 (14), 27 (17). Dictyopterene C′, a colorless oil, had the following properties: $[\alpha]^{22}D$ −12° ($CHCl_3$, *c* 7.32); $[\theta]_{195\,nm}$ −39,000; ir (CCl_4) ν_{max} 3020, 2960, 2930, 2860, 1650, 1455, 1370, 1210 cm^{-1}; proton nmr (benzene-d_6) δ 0.87 (t, 3 H, J = 6.5 Hz), *ca.* 1.26 (m, 6 H), 2.40 (m, 1 H), 2.11 (m, 2 H), 2.58 (m, 1 H, J_{gem} = −20 Hz[20]), 2.84 (m, 1 H, J_{gem} = −20 Hz), *ca.* 5.6 (m, 4 H); carbon-13 nmr δ 14.2 (CH_3), 23.3 (CH_2), 28.8 (CH_2), 29.8 (CH_2), 33.3 (CH_2), 36.5 (CH_2), 37.7 (CH), 127.4 (CH), 128.4 (CH), 129.9 (CH), 136.8 (CH); mass spectrum (70 eV) *m/e* (rel intensity) 150, (15), 135 (2), 121 (5), 115 (3), 106 (12), 93 (50), 91 (83), 79 (100), 77 (77), 67 (22), 66 (22), 65 (39), 55 (12), 53 (22), 51 (22), 41 (60), 39 (64), 29 (33), 27 (43).

If the tetraenes did not separate on the silver nitrate–silica gel column, final purification was achieved by preparative gas chromatography on a 20 ft × 0.375 in. column of 25% Zonyl E-7 on Aeropak 30 (column temperature, 70°; injector temperature, 165°; nitrogen flow rate, 175 ml/min). *trans,trans,cis*-1,3,5,8-Undecatetraene (**17,** fraction 3) had the following spectral properties: uv (*n*-pentane) λ_{max} 245 (sh), 254, 263, 274 nm; proton nmr (benzene-d_6) δ 0.91 (t, 3 H, J = 7.5 Hz), 1.97 (quintet, 2 H, J = 7–7.5 Hz), 2.75 (t, 2 H, J = 6.5 Hz), 4.96 (dd, 1 H, J = 9.5 and 2 Hz), 5.08 (dd, 1 H, J = 16.5 and 2 Hz), 5.34 (dt, 1 H, J = 11 and 6.5 Hz), 5.42 (dt, 1 H, J = 11 and 7 Hz), 5.54 (dt, 1 H, J = 17 and 6.5 Hz), 6.1 (m, 3 H), 6.3 (m, 1 H); carbon-13 nmr[21] δ 30.7 (C-7 methylene); mass spectrum (70 eV) *m/e* 148 (molecular ion). *trans,cis,cis*-1,3,5,8-Undecatetraene (**16,** fraction 4) had the following spectral properties: uv (*n*-pentane) λ_{max} 245 (sh), 254, 263, 274 nm; proton nmr (benzene-d_6) δ 0.89 (t, 3 H, J = 7 Hz), 1.96 (quintet, 2 H, J = 7 Hz), 2.85 (t, 2 H, J = 7 Hz), 4.98 (dd, 1 H, J = 9.5 and 2 Hz), 5.10 (dd, 1 H, J = 17 and 2 Hz), 5.34 (m, 1 H), 5.38 (m, 1 H), 5.39 (m, 1 H), 6.00 (tt, 1 H, J = 11 and 1.5 Hz), 6.13 (m, 1 H), 6.33 (m, 1 H), 6.49 (m, 1 H); carbon-13 nmr[21] δ 26.3 (C-7 methylene); mass spectrum (70 eV) *m/e* 148 (molecular ion).

Molecular distillation of fraction 5 at room temperature (0.001 mm) gave pure **dictyopterene B (6):** $[\alpha]^{24}D$ −43° ($CHCl_3$, *c* 10.1); $[\theta]_{198\,nm}$ +57,000, $[\theta]_{245\,nm}$ −23,000, $[\theta]_{276\,nm}$ +1100; ir (CCl_4) ν_{max} 3080, 3020, 3000, 2960, 2940, 2870, 1630, 1455, 1210 cm^{-1}; uv (95% EtOH) λ_{max} 246.5 nm (ϵ 29,000); proton nmr (benzene-d_6) δ 0.65 (m, 1 H), 0.72 (m, 1 H), 0.92 (t, 3 H, J = 7 Hz), 1.31 (m, 2 H), 2.08 (d of quintets, 2 H, J = 7–7.5 and 1.3 Hz), 4.82 (dd, 1 H, J = 9.5 and 2.6 Hz), 4.96 (dd, 1 H, J = 17 and 2.6 Hz), 5.04 (dd, 1 H, J = 15 and 8.5 Hz), 5.22 (td, 1 H, J = 11.0 and 7.5 Hz), 5.30 (ddd, 1 H, J = 17, 9.5, and 7.5 Hz), 5.89 (tt, 1 H, J = 10.8–11.0 and 1.3 Hz), 6.34 (dd, 1 H, J = 15 and 10.8 Hz); carbon-13 nmr δ 14.4 (CH_3), 15.5 (CH_2), 21.2 (CH_2), 24.5 (CH), 25.2 (CH), 112.2 (CH_2), 124.2 (CH), 128.3 (CH), 131.0 (CH), 136.0 (CH), 140.5 (CH); mass spectrum (70 eV) *m/e* (rel intensity) 148 (12), 133 (2), 119 (13), 117 (7), 115 (6), 105 (30), 91 (95), 79 (100), 77 (53), 67 (28), 66 (26), 65 (24), 56 (16), 54 (25), 52 (22), 41 (61), 29 (13), 27 (31).

A solution of fraction 6 in 0.7 ml of pentane was chromatographed on a 30 ft × 0.375 in. column of 30% DEGS on Chromosorb W (column temperature, 130–140°; injector temperature, 160°; nitrogen flow rate, 165 ml/min) in 0.09-ml portions to give 1.5 mg of **dictyopterene D′ (10):** $[\alpha]^{23}D$ +75° (CH_2Cl_2, *c* 0.15); positive $[\theta]$ at 205 nm; ir (CCl_4) ν_{max} 3010, 2960, 2940, 2900, 2880, 1650, 1630, 1550, 1460, 1270, 1210 cm^{-1}; proton nmr (benzene-d_6) δ 0.89 (t, 3 H, J = 7.5 Hz), 1.97 (quintet, 2 H, J = 7–7.5 Hz), 2.21 (m, 2 H), 2.60 (m, 1 H, J_{gem} = −20 Hz), 2.81 (m, 1 H, J_{gem} = −20 Hz), 3.47 (m, 1 H), 5.30 (m, 1 H, J_{cis} = 10.8 Hz), 5.41 (m, 1 H, J_{cis} = 10.8 Hz), 5.55–5.85 (m, 4 H); carbon-13 nmr δ 14.6 (CH_3), 21.0 (CH_2), 28.8 (CH_2), 33.9 (CH_2), 36.5 (CH), 127.3 (CH), 129.0 (CH), 129.7 (CH), 130.6 (CH), 133.6 (CH), 135.5 (CH); mass spectrum (70 eV) *m/e* (rel intensity) 148 (19), 133 (6), 119 (35), 117 (9), 115 (7), 105 (45), 91 (100), 79 (97), 77 (43), 67 (29), 66 (37), 65 (22), 55 (15), 53 (15), 51 (15), 41 (49), 39 (35), 29 (11), 27 (20).

Comparison of the Essential Oils of *Dictyopteris plagiogramma* and *D. australis*. The two seaweeds were separated from each other by hand and about 1 kg of wet alga was placed in a large vacuum desiccator and subjected to reduced pressure for 4–6 hr. The essential oil and water were condensed in a Dry Ice cooled trap and the condensate was extracted with *n*-pentane. The dried extract was evaporated and the essential oil was analyzed by gas chromatography on a 30 ft × 0.125 in. column of 30% DEGS on Chromosorb W (see above for conditions and retention times). The essential oil of *D. plagiogramma* showed the presence of 16% **2,** 8% **8,** 1.5% **11,** 0.8% **12,** 69% **5** (dictyopterene B rearranges completely on the column at 120°) and **10** combined, 1.5% **16,** and 3% **17.** The essential oil of *D. australis* was composed of the same constituents but by contrast showed the presence of 25% **2,** 30% **8,** 4% **11,** 2% **12,** 36% **5** and **10,** 1.5% **16,** and 1.5% **17.** Percentages were based on peak areas.

Oxidation of Dictyopterenes A and B. Ozonolysis. Dictyopterene A (20 mg) in 5 ml of chloroform was ozonized at −10°. When ozonolysis was complete 3 ml of 30% hydrogen peroxide and 25 mg of potassium carbonate were added and the mixture was stirred for 12 hr at room temperature and then boiled to remove the chloroform. The solution was acidified with dilute sulfuric acid and the organic acids were extracted with five 5-ml portions of ether and then transferred into dilute aqueous ammonium hydroxide. The ammonia solution was evaporated and the proton nmr spectrum of the resulting ammonium salts in H_2O or D_2O showed the presence of ammonium formate (δ 8.93, s), *n*-valerate (δ 1.34, t, 3 H, J = Hz; δ 1.55–2.10, complex multiplet, 4 H; δ 2.65, t, 2 H, J = 7 Hz), and *trans*-1,2-cyclopropanedicarboxylate (δ 1.61 and 2.25, 2 H multiplets of A_2X_2 spectrum). Paper chromatography confirmed the presence of formic, valeric, and cyclopropane-1,2-dicarboxylic acids.

Dictyopterene B (45 mg) was ozonized and worked up oxidatively with hydrogen peroxide as described above. After addition of 0.5 ml of dilute sulfuric acid the reaction mixture was extracted with seven 6-ml portions of ether. The ether solution was extracted with dilute ammonium hydroxide, the ammonia solution was evaporated, and the mixture of ammonium salts was analyzed by nmr spectroscopy. The nmr spectrum in H_2O or D_2O showed the presence of ammonium formate, *trans*-1,2-cyclopropanedicarboxylate, and propionate (δ 1.51, t, 3 H, J = 7 Hz; δ 2.65, q, 2 H, J = 7 Hz).

B. Lemieux Oxidation[3] to 1. Dictyopterene A (490 mg) was dissolved in 50 ml of *t*-BuOH and added dropwise to 425 ml of 0.1 *M* $NaIO_4$ and 0.0024 *M* $KMnO_4$. After 40 hr the solution was reduced with $NaHSO_3$, the pH was then adjusted to 8, and the solution was washed with ether to remove neutral products. Evaporation of the ether extract of the acidified solution yielded 250 mg of solid which was dissolved in 1 ml of 50% chloroform–methanol and applied to a 1.6 × 101 cm column of Sephadex LH-20. Elution was continued with 50% chloroform–methanol and 5-ml fractions were collected. Fractions 43–46 yielded (*S,S*)-*trans*-cyclopropane-1,2-dicarboxylic acid (**1**), which after two recrystallizations from dilute hydrochloric acid gave 36 mg of pure **1,** mp 168–170° (reported[4] mp 169.5–170°), $[\alpha]^{25}D$ +230° (H_2O, *c* 0.747) [reported[4] $[\alpha]^{25}D$ +227.8° (EtOH, *c* 2.342), 96.3% optical purity].

Compound **1** was also obtained by a similar oxidation of dictyopterene B.

Cope Rearrangement of Dictyopterene A to 3. A solution of 160 mg of pure dictyopterene A and 20 ml of hexane in a sealed 1 × 30 cm thick-wall (2 mm) Pyrex tube was heated to *ca.* 165° in an oven for 48 hr. The hexane was evaporated *in vacuo* to yield 158 mg of (*S*)-6-butylcyclohepta-1,4-diene (**3**) as a clear, colorless oil, $[\alpha]^{21}D$ +2.0° ($CHCl_3$, *c* 15.8). No dictyopterene A could be detected in **3** by gas chromatography.

In another experiment 160 mg of dictyopterene A and 4 ml of hexane were sealed in a Pyrex tube and heated at *ca.* 160–175° for 2.8 hr. After removal of most of the hexane *in vacuo,* compound **3** and unreacted dictyopterene A were separated by preparative gas chromatography on a 30 ft × 0.375 in. column of 30% DEGS on Chromosorb W (column temperature, 125°; injector temperature, 160°; nitrogen flow rate, 165 ml/min) to give 96 mg of optically purer **3,** $[\alpha]^{23}D$ +3.0° ($CHCl_3$, *c* 9.6), and 26 mg of partially ra-

cemized dictyopterene A, $[\alpha]^{23}D$ +26° ($CHCl_3$, c 2.6).

Cope Rearrangement of Dictyopterene B to 5. A solution of dictyopterene B (350 mg) and 4 ml of pentane in a sealed Pyrex tube was heated to 103–108° for 40 hr. The pentane was evaporated and the yellow liquid was molecularly distilled[19] at room temperature (2×10^{-2} Torr) to give 340 mg of (*R*)-6-(*cis*-but-1′-enyl)-cyclohepta-1,4-diene (**5**) as a clear, colorless oil, $[\alpha]^{23}D$ −24° ($CHCl_3$, c 14.3).

Partial Diimide Reduction of 5 to 3. Compound **5** (1.3 g) was dissolved in 100 ml of methanol and 2 ml of hydrazine hydrate containing a few milligrams of cupric sulfate. Air was passed through this mixture for 1 hr, an additional 2 ml of hydrazine hydrate was then added, and aeration was continued for another 0.5 hr. From the sparingly soluble oil which separated on concentration of the solution *in vacuo*, 20 mg of compound **3**, $[\alpha]D$ +3° ($CHCl_3$, c 2) (*ca.* 2%), was isolated by gas chromatography on a 30 ft × 0.375 in column of 30% DEGS on Chromosorb W (column temperature 135°; nitrogen flow rate, 200 ml/min; 16–60 μl injections). The proton nmr spectrum and CD curve of the product were identical with those of **3** obtained from Cope rearrangement of dictyopterene A.

Ozonolysis of 3. About 195 mg of **3** in 80 ml of ethyl acetate was ozonized almost to completion at −78°. After addition of 20 ml of acetone, the solution was warmed to, and maintained at, −10°. Jones reagent[22] (2.7 g of CrO_3, 2.3 ml of concentrated H_2SO_4, and 10 ml of H_2O) was then added slowly until the formation of a dark precipitate was noted. After addition of 100 ml of water the solution was extracted with ether and the organic acids were then transferred into 3% aqueous sodium hydroxide. The basic solution was acidified and reextracted with ether. Evaporation of the ethereal solution *in vacuo* yielded a yellow oil, partially soluble in water. Crystallization from water yielded 6 mg of (*S*)-butylsuccinic acid (**4**) as colorless crystals, mp 85–86° (reported[6] mp 82.5–83.5), $[\alpha]D$ −3.5° (EtOH, c 0.54) [reported[6] $[\alpha]^{25}D$ −22.5° (H_2O, c 5)], with an optical purity of about 13%.

In a second experiment 85 mg of **3** was dissolved in 3 ml of methylene chloride and ozonized at −10°. The solution was oxidatively worked up with hydrogen peroxide as described above for the ozonolysis of dictyopterene A. Nmr analysis of the ammonium salt of the acidic product in H_2O[23] showed the presence of ammonium malonate (δ 3.60, s).

Ozonolysis of 5. About 70 mg of **10** in 95% ethanol was ozonized and worked up oxidatively as described above for dictyopterene B. Nmr analysis of the resulting ammonium salt mixture in H_2O showed the presence of ammonium formate, acetate (δ 2.39, s), propionate, succinate (δ 2.96, s), and malonate. Presumably the acetate and succinate are formed by decarboxylation of malonic and ethanetricarboxylic acids.

Lemieux Oxidation[3] of Dictyopterene C′ to 7. Oxidation of 650 mg of **5** with sodium metaperiodate–potassium permanganate as described above gave colorless oil which failed to crystallize from water. The dextrorotatory oil was subjected to gel filtration on a 1.6 × 101 cm column of Sephadex LH-20 with 50% chloroform–methanol, 5-ml fractions were collected and from fractions 41–44, crystalline (*R*)-butylsuccinic acid (**7**) was obtained which after recrystallization from water yielded 48 mg of pure **7**: mp 81–82° (reported[6,24] mp 82.5–83.5 and 77–79°); $[\alpha^{25}D$ +18.8° (H_2O, c 4.16) [reported [$\alpha^{25}D$ +23.2° (H_2O, c 1.5),[6] +22.6° (H_2O, c 5),[6] +22.0° (H_2O, c 10),[6] +26.5° (EtOH, c 5.2),[6] and +26.9° (EtOH, c 1.3);[24] proton nmr (D_2O) δ 1.33 (t, 3 H), 1.77 (m, 4 H), 2.03 (m, 2 H), 3.13 (m, 2 H), 3.30 (m, 1 H).

Photoisomerization of the Undecatrienes. Isolation of *cis,trans*-1,3,5-Undecatriene. A 3-ml solution of 0.8 *M* 1,3,5-undecatriene (from IFF) and 0.03 *M* benzophenone in benzene was added to several 13 × 100 mm Pyrex tubes and degassed. Each tube was sealed and the mixture was photolyzed at 25° for 3.5 hr with a 550-W Hanovia medium-pressure Hg lamp equipped with Corning filters 0-52 and 7-60 to allow irradiation with only the 3660-Å Hg line. To the resultant photostationary state mixture of trienes were added 0.25 g of maleic anhydride and *ca.* 5 mg of hydroquinone and the mixture was refluxed for 6 hr. After cooling the benzene solution was applied to a 1 × 24 cm column of alumina and the hydrocarbons were eluted with *n*-pentane. Various fractions were collected and those showing triene ultraviolet absorption were combined and evaporated. Further purification by prepartive gas chromatography on a 20 ft × 0.375 in. column of 25% TCEP on Chromosorb P (column temperature, 115°; injector temperature, 125°; nitrogen flow rate, 150 ml/min) gave *cis,trans*-1,3,5-undecatriene (**13**) as the major component: uv (*n*-pentane) λ_{max} 244 (sh), 253, 263, 273 nm; proton nmr (CCl_4) δ 0.90 (t, 3 H, *J* = 7.5 Hz), 1.31 (br m, 6 H), 2.08 (m, 2 H), 5.05 (dd, 1 H, *J* = 10.2 and 1.5 Hz), 5.13 (dd, 1 H, *J* = 17.1 and 1.5 Hz), 5.76 (dt, 1 H, *J* = 15.6 and 7.2 Hz), 6.0 (m, 2 H), 6.44 (ddt, 1 H, *J* = 15.6, 10.3, and 1.5 Hz), 6.74 (dt, 1 H, *J* = 17.1 and 10.2 Hz); carbon-13 nmr δ 116.9 (C-1 methylene); mass spectrum (70 eV) *m/e* 150 (molecular ion).

No **11** or **12** was present in the maleic anhydride treated 1,3,5-undecatriene as indicated by gas chromatography. A small amount of material having a relative retention time of 1.03 (with respect to **11** as 1.00) was not collected but is probably *cis,cis*-1,3,5-undecatriene. A small amount of *trans,trans,trans*-2,4,6-undecatriene (**15**) having a relative retention time of 1.28 and contaminated with *ca.* 12% of an isomeric 2,4,6-triene (relative retention time 1.25) was collected: uv (*n*-pentane) 247 (sh), 256, 265, 276 nm; ir (CS_2) ν_{max} 970 cm^{-1}; proton nmr (CCl_4) δ 0.89 (br t, 3 H, J_{max} = 7 Hz), 1.31 (br m, 4 H), 1.72 (d, 3 H, *J* = 6.5 Hz), 2.04 (broad q, 2 H, *J* = 7 Hz), 5.5 (br m, 2 H), 6.0 (br m, 4 H); mass spectrum (70 eV) *m/e* 150 (molecular ion). The isomeric 2,4,6-trienes having relative retention times of 1.37 and 1.42 were collected together and were not completely characterized: uv (*n*-pentane) λ_{max} 247 (sh), 259, 268, 278 nm; ir (CS_2) ν_{max} 685, 970 cm^{-1}; proton nmr (CCl_4) δ 0.89 (br t, 3 H, *J* = 7 Hz), 1.31 (br m, 4 H), 1.71 and 1.72 (d, 3 H, *J* = 6.5 Hz), 2.07 (broad q, 2 H, *J* = 7 Hz), 5.3–6.5 (complex multiplets, 6 H); mass spectrum (70 eV) *m/e* 150 (molecular ion).

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Synthesis of Oxytocin and Related Diastereomers Deuterated in the Half-Cystine Positions. Comparison of Solid-Phase and Solution Methods[1,2]

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Four derivatives of the neurohypophysial hormone oxytocin deuterated at the α and β positions of the two half-cystine residues have been synthesized. The substituted amino acid Boc-*S*-benzyl-DL-[α,β,β-$^2H_3$]cysteine was used to prepare [1-hemi-DL-[α,β,β-$^2H_3$]cystine]oxytocin and [6-hemi-DL-[α,β,β-$^2H_3$]cystine]oxytocin. The diastereomeric mixtures were separated and purified by partition chromatography and gel filtration to give [1-hemi-L-[α,β,β-$^2H_3$]cystine]oxytocin, [1-hemi-D-[α,β,β-$^2H_3$]cystine]oxytocin, [6-hemi-L-[α,β,β-$^2H_3$]cystine]oxytocin, and [6-hemi-D-[α,β,β-$^2H_3$]cystine]oxytocin. The former two compounds were prepared by both solid-phase and solution techniques of peptide chemistry, and the two methods were compared in the synthesis of these derivatives. The solid-phase method was considerably faster and gave better overall yields, while the solution method permitted a slightly more conservative use of deuterated amino acid. It was found that much shorter deprotection and coupling times and much smaller excesses of amino acid were compatible with the solid-phase methodology.

The preparation of amino acids, polypeptides, peptide hormones, and proteins specifically labeled in *nonexchangeable* positions by deuterium is of considerable utility for various chemical, biological, and physical studies. For example, partially deuterated derivatives have been utilized in studies of protein structure, functions, and folding.[3-7] The microdynamical behavior of the neurohypophysial peptide hormones in solution[8,9] and the interaction of these hormones with their biological carrier proteins the neurophysins have been studied utilizing the deuterium label.[9] Deuterated derivatives have also proven very useful for the unambiguous assignment of proton[10-14] and carbon-13[15,16] resonances in nuclear magnetic resonance spectroscopy studies of peptides,[10-12,15,16] peptide hormones,[13-16] and related compounds. Since many of the physical[11-16,17-19] properties and biological activities[20-22] of these compounds are not significantly affected by the perturbation of deuteration, it appears likely that partially deuterated amino acids, peptides, and proteins will find increased utility.

We report here the total synthesis of four partially deuterated derivatives of the posterior pituitary hormone, oxytocin (**1**) (Figure 1) in which the protons on the α and β carbons of the half-cystine residues (positions 1 and 6, Figure 1) have been replaced by deuterons. Since both the hemi-D-cystine and hemi-L-cystine isomers of each of the half-cystine residues were desired, we synthesized [1-hemi-DL-[α,β,β-$^2H_3$]cystine]oxytocin (**2**) and [6-hemi-DL-[α,β,β-$^2H_3$]cystine]oxytocin (**3**) and separated the diastereomeric pairs by partition chromatography on Sephadex G-25.[23,24] The [1-hemi-DL-[α,β,β-$^2H_3$]cystine]oxytocin was synthesized by solid-phase peptide synthesis (SPPS) using the standard chloromethylated resin,[25,26] and by solution methods. In view of the current interest in labeled peptides and the desirability of fast, efficient synthetic routes to these and other peptides, these synthetic studies offered a convenient comparison of the two techniques. The [6-hemi-DL-[α,β,β-$^2H_3$]cystine]oxytocin was synthesized by solid-phase methods only. Of special interest was the use of SPPS in cases where the usual large excesses[25,26] of amino acid used in coupling (two to four times stoichiometric) could be avoided and the valuable deuterated amino acids could be conserved.

The solid-phase synthesis of [6-hemi-DL-[α,β,β-$^2H_3$]cystine]oxytocin (**3**) was carried out on a semiautomated device with the methodology shown in Table I. One coupling with a 2.5-fold excess of amino acid and DCC was used for each of the amino acids except for the deuterated cysteine.

The Boc-*S*-benzyl-DL-[α,β,β-$^2H_3$]cysteine (**4**) was only the fourth residue in this synthesis. Its coupling was varied somewhat in that two couplings were employed using