Austradiol Acetate and Austradiol Diacetate, 4,6-Dihydroxy-(+)-selinane Derivatives from an Australian *Laurencia* sp.

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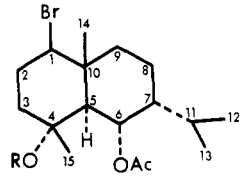
Received March 18, 1982

The structures of austradiol acetate and diacetate are established as 1 and 2 by chemical and spectroscopic analysis. Several unusual stereochemical features of these molecules are discussed.

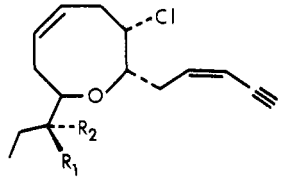
The *Laurencia* genus of red algae elaborates a wide variety of sesquiterpenoids among which eudesmane (selinane) representatives are occasionally encountered.[1] While investigating the extracts of a Western Australian collection of *Laurencia filiformis*, we have isolated a new member of the eudesmane group with interesting stereochemical aspects.

Austradiol acetate (1) was the major sesquiterpenoid component of an extract in which austradiol diacetate (2),



1, R=H

2, R=Ac



3, R_1=Br, R_2=H

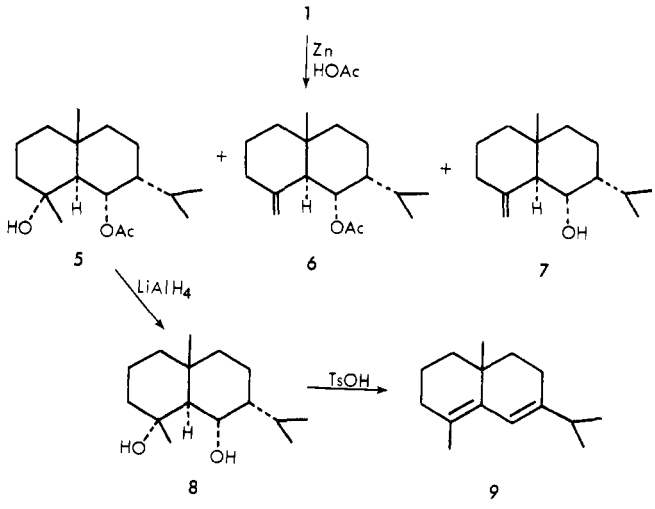
4, R_1=H, R_2=Br

cis-dihydrorhodophytin (3), and *cis*-epidihydrorhodophytin (4) were also found.[1] Column and high-pressure liquid chromatography (HPLC) afforded 1 as an oil, $[\alpha]^{22}_D$ +14.5°. The presence of a hydroxyl group (3590, 3480 cm^{-1}), a carbonyl group (1750 cm^{-1}), and a *gem*-dimethyl group (1390, 1365 cm^{-1}) was indicated by the IR spectrum. The ^1H NMR spectrum of 1 showed the *gem*-dimethyl group to be contained in an isopropyl moiety (d, δ 0.93 and 1.00, each 3 H, J = 6.5 Hz), identified the carbonyl as an acetoxy group (δ 2.04, 3 H, s), and supported the presence of a hydroxyl group (δ 3.32, 1 H, br s, exchangeable with D_2O). In addition, two tertiary methyls (δ 1.13, 6 H, s), a bromomethine hydrogen (δ 3.88, dd, J = 7, 8.5 Hz), and an acetoxy methine (δ 5.31, dd, J = 3.5, 11.8 Hz) were evident in the ^1H NMR spectrum. Confirmation of these functionalities was provided by ^{13}C NMR absorptions at δ 65.9 (d, HCBr), 71.0 (s, COH), 77.3 (d, HCOAc), and 168.8 (s, CO=O).

Neither the CI nor the EI mass spectrum showed a molecular ion for 1. Strong M – 18 (m/z 342, 344) and M – 60 (m/z 300, 302) ions were observed, however, as well as nonbromine-containing peaks at m/z 221 (M – 60 – 79), 220 (M – 60 – 80), and 203 (M – 60 – 79 – 18). An intense metastable ion at m/z 186.4 indicated that the m/z 203 peak was derived from that at m/z 221, thus supporting a molecular weight of 360. The high-resolution CI mass spectrum established the formula of $C_{17}H_{28}O_2Br$ for the M + 1 – 18 fragment and thus $C_{17}H_{29}O_3Br$ for 1.

LIS studies in the ^1H NMR spectrum permitted the assignment of the C-3 through C-7 sequence of 1. With complexation at the C-4 hydroxyl, the following absorptions were revealed: a doublet (H-5, J = 11.8 Hz), partially

Scheme I



hidden by the peak at δ 2.04 in the nonshifted spectrum, a multiplet, which was initially buried in the δ 1.6–1.8 envelope ($H_{3\alpha}$ and $H_{3\beta}$), and the singlet for the C-4 methyl geminate to the hydroxyl. Decoupling of the shifted spectrum confirmed the vicinal diaxial relationship of the bridgehead hydrogen, H-5, and the acetoxy methine, H-6. The remaining small coupling of the acetoxy methine (3.5 Hz) requires a cis relationship to an adjacent methine at C-7 and hence an axial arrangement for the isopropyl group at that carbon.

The eudesmane skeleton for 1, suggested by its spectral data, was established by conversion to (+)-δ-selinene (9). Debromination of 1 with zinc and acetic acid (Scheme I) gave a mixture of debromoaustradiol acetate (5), the dehydrated analogue 6, and the dehydrated saponified analogue 7. The latter was also obtained by $LiAlH_4$ reduction of 6. $LiAlH_4$ reduction of 5 afforded diol 8, dehydration of which gave (+)-δ-selinene (9)[2] in 43% yield. Thus, both the skeletal structure and absolute configuration of 1 are established.

In analogy with other *Laurencia* bromoeudesmanes, it was expected that the bromine was located at C-1. Evidence in support of this assignment as well as its cis relationship to the angular methyl at C-10 comes from an NMR comparison of 1 and 5. The angular methyl group (C-14) of 1 is deshielded in the ^1H NMR spectrum (δ 1.13 vs. 1.00 for 5) and shielded in the ^{13}C NMR spectrum (δ 15.5 vs. 19.5 for 5). Furthermore, the downfield shift of C-1 (Δ 24.3 ppm) and C-2 (Δ 11.9 ppm) and the upfield shift of C-9 (Δ 2.0 ppm) in 1 compared to that in 5 is expected for insertion of an equatorial bromine at C-1.[3-5]

(1) Erickson, K. L. In "Marine Natural Products"; Scheuer, P. J., Ed.; Academic Press: New York, Vol. V, in press.

(2) Sun, H. H.; Erickson, K. L. *J. Org. Chem.* **1978**, *43*, 1613.

(3) Dalling, D. K.; Grant, D. M.; Paul, E. G. *J. Am. Chem. Soc.* **1973**, *95*, 3718.

(4) Schneider, H.; Hoppen, V. *J. Org. Chem.* **1978**, *43*, 3866.

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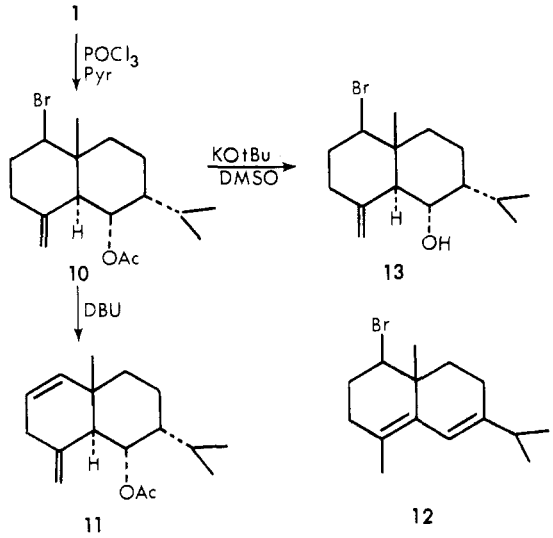
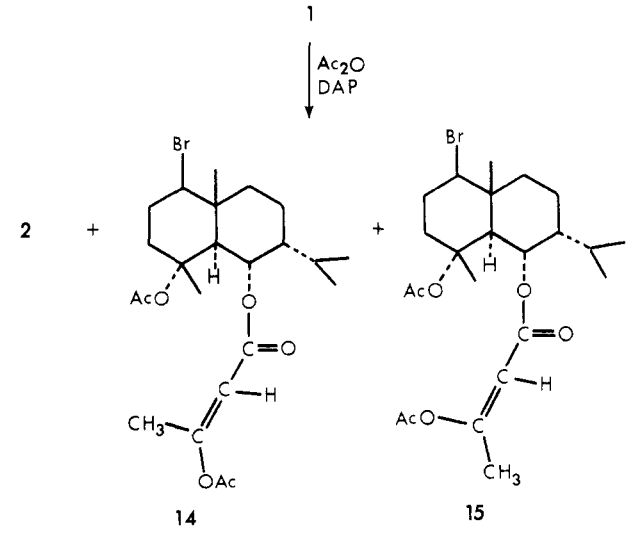
Scheme II



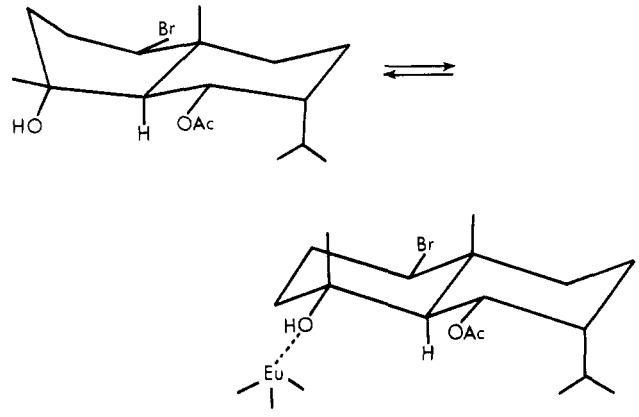
Scheme III



Chemical evidence for the placement of the bromine at C-1 is provided in Scheme II. Dehydration of **1** with $POCl_3$/pyridine gave the exocyclic olefin **10** whose olefinic hydrogens appeared at δ 4.26 and 4.78 in the ^1H NMR spectrum. The acetoxy methyl, residing in the shielding region of the double bond, appeared at δ 1.88. (This shielding effect on the acetoxy methyl is also observed in **6**.) Dehydrobromination of **10** with DBU at 105 °C (4 days) afforded diene **11**. The doubly allylic hydrogens appeared at δ 2.91 (H-3α) and 2.68 (H-3β) in the ^1H NMR spectrum and were coupled to the exocyclic olefinic hydrogens at δ 4.40 and 4.92. The acetoxy methine, the bridgehead hydrogen at C-5, and the exocyclic vinyl hydrogens in **11** were deshielded relative to their positions in monoenes **6** and **10**.

Olefin **10** was also obtained from **1** on refluxing with *p*-toluenesulfonic acid (benzene) along with bromo diene **12**.[6] In an attempt at dehydrobromination of **10** with KO-*t*-Bu/Me_2SO, bromo alcohol **13** was produced in quantitative yield. An interesting feature is observed in comparing the chemical shifts of the olefinic protons in **10** and **13** and in **6** and **7**. In either CCl_4 or $CDCl_3$, the presence of an acetoxy group at C-6 confers a much greater shift differential between the two olefinic hydrogens (Δ 0.52 ppm for **10** and Δ 0.57 ppm for **6**) than does a C-6 hydroxyl group (Δ 0.28 ppm for **13** and Δ 0.31 ppm for **7**). In analogous compounds (junenol and its acetate), in which the C-7 isopropyl group is equatorial, the olefinic hydrogens experience the same shift differential (Δ 0.30 ppm in $CDCl_3$) in both the alcohol and the acetate.[7] The replacement of the C-6 acetoxy groups by a hydroxyl group also induces a slight deshielding of one of the axial isopropyl methyl groups.

The equatorial nature of the tertiary hydroxyl group at C-4 in **1** was established by the fact that the axial methyl at C-10 was not appreciably shifted in the LIS ^1H NMR studies. The axial nature of both the isopropyl and the C-4 methyl groups is unusual for natural eudesmanes. The diaxial interaction of the C-4 and C-10 methyl substituents, coupled with the C-4 and C-6 oxygen dipole–dipole interaction, results in the bromohydrin ring of **1** adopting a twist conformation. When the C-4 hydroxyl complexes with the europium shift reagent, this ring reverts to the chair form. This conformational change can be followed



by observing the change in coupling constants for the bromomethine hydrogens as shift reagent is added. The initial values of 7 and 8.5 Hz for the twist conformation are replaced by values of 4 and 12 Hz in the chair conformation.[8-10] The latter values are those expected for an equatorial bromine substituent.

Crystalline austradiol diacetate (**2**) was obtained as a minor component of the extract. It, too, provided no parent ion in the mass spectrum, but ions at m/z 343, 345 (M − 59), 300, 302 (M − 60 − 42) and 282, 284 (M − 60 − 60) suggested that it differed from **1** only by an acetoxy group. The ^1H NMR spectrum of **2** displayed a second acetoxy methyl at δ 1.86[11] and a 1.25-ppm downfield shift of the bridgehead hydrogen at C-5 relative to that in **1**.

Austradiol diacetate (**2**) was synthesized (in poor yield) from **1** upon treatment with acetic anhydride in the presence of 4-(dimethylamino)pyridine (Scheme III). The major products of this reaction were **14** and **15**, resulting from an aldol condensation at the secondary acetoxy methyl group followed by acetylation of the resulting enol. The mass spectra of these materials established their molecular weight at 486. Four singlets at low field in the

(5) Pekhk, T. I.; Lippmaa, E. T.; Lysenkov, V. I.; Bardyshev, I. I. *Zh. Org. Khim.* **1979**, *15*, 1694.
(6) For enantiomer see: Howard, B. M.; Fenical, W. *J. Org. Chem.* **1977**, *42*, 2518.
(7) Niwa, M.; Iguchi, M.; Yamamura, S. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3145.
(8) Williamson, K. L.; Johnson, W. S. *J. Am. Chem. Soc.* **1961**, *83*, 4623.
(9) Brown, E. D.; Solomon, M. D.; Sutherland, J. K.; Torre A. *J. Chem. Soc., Chem. Commun.* **1967**, 111.
(10) Suzuki, M.; Furusaki, A.; Kurosawa, E. *Tetrahedron* **1979**, *35*, 823.
(11) Lichtenthaler, F. W.; Emig, P. *Tetrahedron Lett.* **1967**, 577.

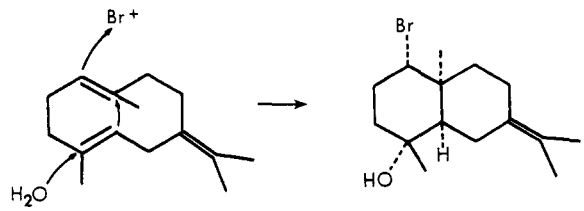
Table I. ^{13}C NMR Spectral Data

carbon	chemical shift, δ				
	1[a]	5[a]	11[b]	14[a]	15[a]
1	65.9 (d)	41.6 (t)	139.4 (d)	65.1 (d)	65.2
2	31.1 (t)	19.2 (t)	123.7 (d)	31.3 (t)	31.2
3	41.9 (t)	41.6 (t)	33.3 (t)	37.9 (t)[c]	38.0[c]
4	71.0 (s)	71.9 (s)	143.4 (s)	84.3 (s)	83.9
5	51.0 (d)	51.0 (d)	47.9 (d)	45.8 (d)[d]	46.4[d]
6	77.3 (d)	77.9 (d)	72.3 (d)	73.9 (d)	73.8
7	43.8 (d)	44.4 (d)	43.7 (d)	44.5 (d)[d]	44.3[d]
8	22.9 (t)	23.2 (t)	22.9 (t)	22.6 (t)	22.4
9	37.1 (t)	39.1 (t)	37.5 (t)	37.6 (t)[c]	37.7[c]
10	41.9 (s)	37.3 (s)	39.5 (s)	42.5 (s)	42.3
11	23.9 (d)	24.0 (d)	24.3 (d)	23.5 (d)	23.6
12	22.1 (q)	22.3 (q)	22.3 (q)	22.1 (q)	22.1
13	25.1 (q)	25.3 (q)	25.6 (q)	25.3 (q)	25.4
14	15.5 (q)	19.5 (q)	20.8 (q)	16.6 (q)	16.7
15	23.1 (q)	23.4 (q)	107.5 (t)	21.9 (q)[e]	21.5[e]
16 (1′)	168.8 (s)	169.3 (s)	169.9 (s)	165.2 (s)	162.7
17 (2′)	21.7 (q)	21.9 (q)	21.1 (q)	112.0 (d)	110.1
18 (3′)				163.0 (s)	159.1
19 (4′)				17.9 (q)	20.9[e]
20, 21 (3-OAc)				168.0 (s)	167.8
				21.1 (q)[e]	21.5[e]
22, 23 (4-OAc)				170.4 (s)	170.3
				21.6 (q)[e]	21.5[e]

[a] $CDCl_3$. [b] C_6D_6. [c-e] Assignments may be interchanged.

^{13}C NMR spectra (Table I) were ascribed to the two acetoxy carbonyls, the butenoate carbonyl, and the acetoxy-bearing vinyl carbon. The second vinyl carbon appeared as a doublet in the olefin region (δ 112.0 for **14** and δ 110.1 for **15**).[12] ^{13}C NMR assignments were facilitated by comparison with the spectra of both the *E* and *Z* isomers of ethyl 3-acetoxy-2-butenoate (independently synthesized[13]). The ^1H NMR assignments of the butenoate side chains of **14** and **15** were made in analogy to those reported[14] for the ethyl 3-acetoxy-2-butenoates and are found in Table II.

Austradiol acetate (**1**) and diacetate (**2**) possess an unprecedented trans relationship between the bromine at C-1 and the oxygen function at C-4. All other cyclohexyl 1,4-bromohydrins isolated from marine sources (including noneudesmane derivatives) display a cis relationship between these two groups. The presumed biogenesis of these systems is that of a bromonium ion induced cyclization of a diene precursor (germacrene in the case of the eudesmanes simultaneous with water attack:



A trans relationship of these two groups in the case of **1** and **2** implies that the concerted addition is occurring with a different conformation of the germacrene precursor or that the process is nonsynchronous. Water could add after the cyclization process, for example, to an olefin intermediate such as **10**. Although the number of compounds involved is not large, it may be significant that all of the (+)-eudesmanes previously isolated from *Laurencia* species possess a vinyl carbon at C-4, while the (−)-eudesmanes from *Laurencia* possess a hydroxyl at C-4, and that hydroxyl is cis to the C-1 bromine. The austradiol acetates are the exception.

Experimental Section

UV spectra were measured by using a Hitachi EPS-3T spectrometer. IR spectra were recorded on a Hitachi 257 spectrometer. ^1H NMR spectra were recorded on Varian 24B, JEOL JNH-MH-100, and Bruker Cryospec WM-250 spectrometers with Me_4Si as an internal reference in CCl_4 solvent unless otherwise indicated; *J* values are given in hertz. The ^{13}C NMR spectra were obtained on JEOL FX-60 and Bruker Cryospec WM-250 spectrometers at 15.04 and 62.90 MHz, respectively. Mass spectra were obtained on a VG Micromass 7070 system. Optical rotations were measured in $CHCl_3$ on a JASCO DIP-4 polarimeter. HPLC was performed on a Waters system by using a Whatman Partisil M9 10/50 silica gel column. Merck 7736 silica gel H (Type 60) was used for shorty funnel chromatography. Merck 5715 TLC plates (silica gel 60 F_{254}, precoated, 0.25-mm layer thickness) were used for both analytical and preparative analyses.

Isolation. Freeze-dried alga[15] (642 g) was extracted successively with petroleum ether, dichloromethane, and ethyl acetate. The petroleum ether extract (1.3 g) and the combined dichloromethane and ethyl acetate extract (4.9 g) were each funnel chromatographed through silica gel (TLC grade), eluted under vacuum with a solvent gradient system from petroleum ether to dichloromethane to ethyl acetate. The 5% $EtOAc/CH_2Cl_2$ fractions were further partitioned by HPLC, with 10% and 20% $EtOAc/CH_2Cl_2$ as the eluant, to give **2** as white crystalline rosettes (40 mg, 0.006% of dry wt) and **1** as a colorless oil (1.2 g, 0.18% of dry wt).

Austradiol acetate (1): $C_{17}H_{29}O_3{}^{79}Br$; M_r = 360; $[\alpha]^{22}_D$ +14.5° (*c* 1.75, $CHCl_3$); CI (isobutane) mass spectrum, *m/z* 343.1274 (M + 1 − 18) for $C_{17}H_{28}O_2{}^{79}Br$ (calcd 343.1270) and 345.1245 for $C_{17}H_{28}O_2{}^{81}Br$ (calcd 345.1250); EI mass spectrum, *m/z* (relative intensity) 342/344, 300/302, 285/287 (1), 282/284, 267/269,

(12) (a) Brouwer, H.; Stothers, J. B. *Can. J. Chem.* **1972**, *50*, 601. (b) Matter, U. E.; Pascual, C.; Pretsch, E.; Pross, A.; Simon, W.; Sternhell, S. *Tetrahedron* **1969**, *25*, 691.

(13) (a) Ono, N.; Yoshimura, T.; Saito, T.; Tamura, R.; Tanikaga, R.; Kaji, A. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1716. (b) Casey, C. P.; Marten, D. F. *Tetrahedron Lett.* **1974**, 925. (c) Filler, R.; Naqvi, S. M. *Tetrahedron* **1963**, *19*, 879. ^{13}C NMR ($CDCl_3$) for the *E* isomer, δ 168.0, 165.8, 163.6, 110.1, 60.1, 21.0, 18.0, 14.2; for the *Z* isomer, δ 166.9, 162.9, 159.6, 107.4, 59.2, 20.8, 20.0, 13.5.

(14) Sifniades, S. *J. Org. Chem.* **1975**, *40*, 3562.

(15) The alga was collected on the harbor breakwater at the subtidal fringe, Yanchep, Western Australia, Dec 4, 1979. Reference specimens are in the N.S.W. National Herbarium, Sydney, Australia.

Table II. ^{1}H NMR Spectral Data[a]

proton	chemical shift, δ (J, Hz) 1	2	5	6
1	3.88 (dd, J = 7, 8.5)	3.97 (dd, J = 7.5, 8.5)		
2				
3		2.15 (dd, J = 3, 8)		
		2.48 (m)		
5	2.00 (d, J = 11.8)	3.25 (d, J = 11.5)	1.88 (d, J = 12)	2.25 (d, J = 12)
6	5.31 (dd, J = 3.5, 11.8)	5.31 (dd, J = 4, 11.5)	5.19 (dd, J = 4, 12)	5.01 (dd, J = 4.5, 11)
12	0.93 (d, J = 6.5)	0.92 (d, J = 6.2)	0.93 (d, J = 6)	0.92 (d, J = 6)
13	1.00 (d, J = 6.5)	0.94 (d, J = 6.2)	0.99 (d, J = 6)	0.97 (d, J = 6)
14	1.13 (s)	1.16 (s)	1.00 (s)	0.85 (s)
15	1.13 (s)	1.27 (s)	1.06 (s)	4.14 (br s)
				4.71 (br s)
4-OH	3.32 (br s)		3.22 (s)	
4-OAc		1.86 (s)		
6-OAc	2.04 (s)	1.93 (s)	2.02 (s)	1.88 (s)

proton	chemical shift, δ (J, Hz) 7	8[b]	9	10
1				3.99 (m)
5	2.10 (d, J = 11)	1.70 (d, J = 11.5)		2.32 (d, J = 11)
6	3.97 (dd, J = 5, 11)	4.25 (dd, J = 4.5, 11.5)	6.07 (br s)	5.08 (dd, J = 11)
12	0.93 (d, J = 6)	0.93 (d, J = 6)	1.06 (d, J = 6)	0.93 (d, J = 6)
13	1.07 (d, J = 6)	1.09 (d, J = 6)	1.06 (d, J = 6)	0.98 (d, J = 6)
14	0.80 (s)	0.94 (s)	0.91 (s)	0.94 (s)
15	4.63 (br s), 4.94 (br s)	1.32 (s)	1.66 (s)	4.26 (br s), 4.78 (br s)
4-OH		3.46 (s)		
6-OAc				1.88 (s)
6-OH	3.84 (br s)	3.62 (br s)		

proton	chemical shift, δ (J, Hz) 11	12	13
1	5.50 (s)	4.01 (dd, J = 4.5, 11)	4.05 (br m)
2	5.50 (s)		
3	2.68 (d, J = 19), 2.91 (br d, J = 19)		
5	2.60 (d, J = 12)		
6	5.25 (dd, J = 4.5, 12)	5.92 (br s)	4.05 (br m)
12	0.95 (d, J = 6)	1.04 (d, J = 6)	0.94 (d, J = 6)
13	0.99 (d, J = 6)	1.04 (d, J = 6)	1.08 (d, J = 6)
14	0.92 (s)	1.01 (s)	0.91 (s)
15	4.40 (br s), 4.92 (br s)	1.64 (s)	4.78 (br s), 5.06 (br s)
6-OAc	1.94 (s)		

proton	chemical shift, δ (J, Hz) 14	15
1	4.01 (dd, J = 7, 8)	3.99 (dd, J = 7, 8)
5	3.45 (d, J = 12)	3.30 (d, J = 12)
6	5.30 (dd, J = 4, 12)	5.28 (dd, J = 4, 12)
12	0.92 (d, J = 6)	0.91 (d, J = 6)
13	0.94 (d, J = 6)	0.92 (d, J = 6)
14	1.16 (s)	1.14 (s)
15	1.28 (s)	1.27 (s)
4-OAc	1.87 (s)	1.88 (s)
2′	5.38 (s)	5.30 (s)
4′-CH_3	2.23 (s)	1.91 (s)
3′-OAc	2.08 (s)	2.12 (s)

[a] CCl_4 unless otherwise noted. [b] $CDCl_3$.

257/259, 239/241, 221 (7), 220 (12), 203 (3), 177 (2.5), 162 (10), 137 (100), 81 (48), 43 (47); IR (film) 3590, 3480, 2965, 2880, 1750, 1460, 1390, 1365, 1220, 1030, 703 cm^{-1}; ^{1}H NMR (CCl_4), Table II; ^{1}H NMR ($CDCl_3$) δ 0.91 (3 H, d, J = 6.5), 0.98 (3 H, d, J = 6.5), 1.12, 1.16, 2.06 (each 3 H, each s), 2.08 (1 H, d, J = 11.5), 3.10 (1 H, br s), 3.91 (1 H, dd, J = 7, 9), 5.35 (1 H, dd, J = 3.5, 11.5); ^{1}H NMR (C_6D_6) δ 0.75 (3 H, d, J = 6), 0.90 (3 H, d, J = 6), 0.92 (3 H, s), 1.04 (3 H, s), 1.52 (3 H, s), 1.88 (1 H, d, J = 11.5), 3.58 (1 H, dd, J = 7, 8.5), 5.35 (1 H, dd, J = 3.5, 11.5); ^{13}C NMR ($CDCl_3$), Table I.

Austradiol diacetate (2): $C_{19}H_{31}O_4{}^{79}Br$; M_r = 402; EI mass spectrum, m/z (relative intensity) 343/345 (1, M − 59), 300/302 (7), 282/284 (48), 267/269 (3), 257/259 (2), 239/241 (14), 221 (9), 220 (5), 203 (24), 159 (15), 147 (9), 137 (54), 81 (39), 43 (100); ^{1}H NMR, Table II.

Debromination of 1. Austradiol acetate (97 mg) was reduced with Zn dust (two 0.75-g portions) in acetic acid in a 75 °C bath for 1.5 h. Ether was added to the cooled reaction mixture, and excess Zn was removed by filtration. The ether solution was washed with aqueous $NaHCO_3$ and brine and dried over $MgSO_4$. After filtration the solvent was removed in vacuo to give 73 mg of oil. Preparative TLC (once with CH_2Cl_2) gave 29 mg of **6** (41%) and 4 mg of **7** (6%). Redevelopment of the remaining plate (once with CH_2Cl_2) gave 18 mg of **5** (24%). For **5**: CI mass spectrum [i-C_4H_{10} + $(CH_2NH_2)_2$], m/z (relative intensity) 343 (13) (M + 61), 265 (90) (M + 1 − 18), 223 (20) (M + 1 − 60), 205 (100) (M + 1 − 18 − 60); ^{1}H NMR (CCl_4), Table II; ^{1}H NMR ($CDCl_3$) δ 0.90 (3 H, d, J = 6), 0.97 (3 H, d, J = 6), 0.98 (3 H, s), 1.13 (3 H, s), 1.97 (1 H, d, J = 12), 2.05 (3 H, s), 3.68 (1 H, s), 5.28 (1 H, dd, J = 4, 12); ^{13}C NMR, Table I. For **6**: ^{1}H NMR, Table II.

Reduction of 6. Lithium aluminum hydride was added to a solution of 6 (40 mg) in anhydrous THF. The mixture was refluxed for 26 h. Ether was added, and the solution was washed with 1 M H_2SO_4, saturated $NaHCO_3$, and brine. After the mixture was dried over $MgSO_4$, the ether was removed in vacuo. Preparative TLC of the residue gave 7: 24 mg; EI mass spectrum, m/z (relataive intensity) 222 (M^+, 6), 207 (4), 204 (26), 191 (7), 189 (7), 179 (10), 161 (45), 109 (100); ^1H NMR, Table II.

Reduction of 5. Zinc/acetic acid reduction of 1 (50 mg) gave, after the workup, 33 mg of a debrominated mixture (5-7), which was treated with $LiAlH_4$ in refluxing THF for 4.5 h. After the usual workup, preparative TLC afforded 7 (9 mg, 29%) and 8 (11 mg, 33%). For 8: crystalline; CI mass spectrum [i-C_4H_{10} + $(CH_2NH_2)_2$], m/z (relative intensity) 301 (M + 61, 67), 283 (5), 265 (11), 223 (100), 205 (85), 121 (62); EI mass spectrum, m/z (relative intensity) 222 (M - 18, 20), 207 (37), 204 (5), 189 (8), 179 (7), 161 (11), 137 (100), 121 (23), 109 (44), 95 (28), 81 (56), 43 (72); ^1H NMR, Table II.

Dehydration of 8: (+)-δ-Selinene (9). A catalytic amount of p-toluenesulfonic acid was added to a benzene solution of 8 (11 mg). The mixture was refluxed for 45 min. Ether was added, and the organic phase was washed with saturated $NaHCO_3$ and brine. After the mixture was dried over $MgSO_4$, the solvent was removed in vacuo. Preparative TLC of the crude product (petroleum ether) gave 4 mg (43%) of (+)-δ-selinene (9): $[\alpha]^{24.5}_D$ +195° (c 0.49, $CHCl_3$); EI mass spectrum, m/z (relative intensity) 204 (M^+, 93), 189 (100), 161 (93), 147 (13), 133 (27), 119 (21), 105 (34), 95 (22), 91 (32), 81 (21), 55 (17), 40 (36); UV (EtOH) λ_{max} 234 nm (sh), 248.5, 256 (sh); ^1H NMR, Table II.

Dehydration of 1 with $POCl_3$. Phosphorus oxychloride (130 μL in five portions, 10.5-fold excess) was added to a solution of 1 (47 mg) in pyridine (0.7 mL) during a total reaction time of 19 h at 25 °C and 12 h at 42 °C. When the reaction was complete, ether and ice were added. Pyridine was removed by two 3-mL washes of 3 M HCl. The ether solution, after being washed with saturated $NaHCO_3$ and brine, was dried over $MgSO_4$. After filtration, the ether was removed in vacuo. Preparative TLC (once with CH_2Cl_2) gave 38 mg of 10 (86%) and 3 mg of starting material. Yields were lower without a large excess of $POCl_3$. For 10: EI mass spectrum, m/z (relative intensity) 342/344 (M^+, 1), 282/284 (49), 267/269 (3), 263 (2), 254/256 (4), 239/241 (58), 203 (72), 159 (51), 147 (26), 107 (31), 84 (58), 43 (100); IR (KBr) 2960, 2885, 1720, 1650, 1460, 1440, 1390, 1370, 1270, 1260, 1245, 1230, 1030, 885 cm^{-1}; ^1H NMR, Table II.

Dehydrobromination of 10. DBU (1,5-diazabicyclo[5.4.0]-undec-5-ene, 1.5 mL) was added to 42 mg of crude exo olefin 10, and the reaction mixture was heated at 105 °C for 4 days. The resulting gum was slowly dissolved with 3 M HCl (6 mL) and ether. After removal of the acid layer, which was back-washed with fresh ether, the total ether phase was washed with saturated $NaHCO_3$ and brine and dried over $MgSO_4$. After filtration and vacuum removal of the solvent, preparative TLC of the crude (four times with 25% CH_2Cl_2/petroleum ether) gave minimal amounts of two less polar UV-active components and 11 as a faintly yellow oil: 23 mg (71%); EI mass spectrum, m/z (relative intensity) 262 (M^+), 247, 220, 219, 202 (37), 187 (25), 159 (100), 145 (13), 131 (34), 117 (17), 105 (22), 81 (22), 43 (56); ^1H NMR, Table II; ^{13}C NMR, Table I.

Dehydration of 1 with TsOH. A catalytic amount of p-toluenesulfonic acid was added to a solution of 1 (78 mg) in benzene (1 mL). The solution was refluxed on a steam bath for 4.5 h. The reaction was quenched with saturated $NaHCO_3$ and extracted with ether. The ether solution was washed with saturated $NaHCO_3$ and brine and dried over $MgSO_4$. After filtration, the ether was evaporated in vacuo. Preparative TLC (twice with petroleum ether) gave 12 (16 mg). Redevelopment of the remaining plate (once with CH_2Cl_2) gave 10 (38 mg) and 13 (1 mg). For 12:[6] UV λ_{max} 236 nm (ε 4130), 248 (sh, 3710), 257 (sh, 2840), 299 (2180); ^1H NMR, Table II.

Hydrolysis of 10. A solution of 10 (38 mg) in benzene was added to a 9-fold excess of KO-t-Bu in Me_2SO. The mixture was refluxed for 4.5 h. The products were extracted with water and ether. The ether solution was washed with saturated $NaHCO_3$ and brine and dried over $MgSO_4$. After filtration, the ether was removed in vacuo to give a quantitative yield of 13: EI mass spectrum, m/z (relative intensity) 300/302 (M^+, 1), 282/284 (13), 239/241 (10), 221 (10), 203 (39), 187/189 (21), 169 (18), 149 (27), 119 (43), 107 (96), 91 (43), 81 (54), 69 (44), 55 (63), 41 (100); ^1H NMR, Table II.

Acetylation of 1. A solution of 1 (21 mg), pyridine (0.3 mL), acetic anhydride (0.3 mL), and 4-(dimethylamino)pyridine (17 mg) in CCl_4 (3 mL) was allowed to react for 6 days at 25 °C. Ether was added to the mixture, and the organic phase was washed successively with dilute HCl, 10% $NaHCO_3$, and brine solutions. After drying over $MgSO_4$ and filtration, the ether was removed in vacuo. Preparative TLC of the crude product (33 mg; four times with CH_2Cl_2) gave 2 (1 mg, 4%), 14 (14 mg, 49%), and 15 (7 mg, 25%).

14: CI mass spectrum (i-C_4H_{10}) m/z (relative intensity) 487/489 (M + 1, 1), 427/429 (3), 385/387 (1), 343/345 (84), 301/303 (3), 283/285 (59), 263/265 (9), 239/241 (2), 227/229 (4), 221 (13), 205 (29), 203 (100), 145 (36), 127 (19), 103 (9), 85 (25); IR (film) 2970, 2885, 1765, 1730, 1715, 1665, 1460, 1440, 1390, 1365, 1340, 1250, 1225, 1205, 1195, 1110, 1080, 1035, 1020, 900, 865, 700 cm^{-1}; ^1H NMR, Table II; ^{13}C NMR, Table I.

15: CI mass spectrum (i-C_4H_{10}), m/z (relative intensity) 487/489 (M + 1, 1), 427/429 (2), 343/345, (99), 301/303 (3), 283/285 (49), 263/265 (12), 239/241 (2), 227/229 (4), 221 (11), 205 (30), 203 (100), 145 (37), 127 (18), 103 (6), 85 (59); ^1H NMR, Table II; ^{13}C NMR, Table I.

Acknowledgment. We thank Dr. R. J. Wells and the Roche Research Institute of Marine Pharmacology for providing the alga and the facilities for this investigation. We are also grateful to Mr. Frank Shea, Clark University, for providing some of the ^1H and ^{13}C NMR spectra (NSF Equipment Grant DMR-8108697).

Registry No. 1, 82731-83-7; 2, 82731-84-8; 3, 71778-85-3; 4, 82769-15-1; 5, 82731-85-9; 6, 82731-86-0; 7, 82795-50-4; 8, 82731-87-1; 9, 28624-28-4; 10, 82731-88-2; 11, 82731-89-3; 12, 82731-90-6; 13, 82731-91-7; 14, 82740-45-2; 15, 82740-46-3.

Stereocontrolled Synthesis of 20*S* Steroidal Side Chain

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Received December 29, 1981

The diethylaluminum chloride catalyzed ene reaction between (20*E*)-3β-acetoxy-5,17(20)-pregnadiene and methyl propiolate proceeds, stereospecifically, from the α face to yield methyl (20*S*)-3β-acetoxychola-5,16,22-trienoate, albeit at a slower rate than the 20*R* formation from the *Z* isomer. The triene was hydrogenated to yield the known methyl (20*S*)-3β-acetoxycholanoate. Thus, the ene reaction can be used to prepare either 20*R* or 20*S* steroidal side chains.

In the last decade, a wide variety of di- and sesterterpenes and steroids have been reported to have modified isooctyl (cholesterol-type side chains[2,3] and the unit being attached to the polycyclic nucleus with *R* or *S* stereo-

0022-3263/82/1947-3921$01.25/0