Synthetic Studies of Sesquiterpenes with a cis-Fused Decalin System, 4. Synthesis of (+)-5#H-Eudesma-3,11-diene, (-)-5#H-Eudesmane-4#,11-diol, and (+)-5#H-Eudesmane-4#,11-diol, and Structure Revision of a Natural Eudesmane-4,11-diol Isolated from Pluchea arguta

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SYNTHETIC STUDIES OF SESQUITERPENES WITH A CIS-FUSED DECALIN SYSTEM, 4[1]. SYNTHESIS OF (+)-5βH-EUDESMA-3,11-DIENE, (−)-5βH-EUDESMANE-4β,11-DIOL, AND (+)-5βH-EUDESMANE-4α,11-DIOL, AND STRUCTURE REVISION OF A NATURAL EUDESMANE-4,11-DIOL ISOLATED FROM *PLUCHEA ARGUTA*

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ABSTRACT.—The syntheses of (+)-5βH-eudesma-3,11-diene [**1**], (−)-5βH-eudesmane-4β,11-diol [**2**], and (+)-5βH-eudesmane-4α,11-diol [**15**] were carried out by an unambiguous procedure starting from α-santonin. The diene **1** was identical with a natural product which was isolated previously as a termite defense substance. Although structure **2** was recently proposed for a new eudesmane-1,4-diol [**A**] isolated from *Pluchea arguta*, synthetic **2** and its C-4 epimer, **15**, were not identical with this natural eudesmane-4,11-diol when their physical and spectroscopic parameters were compared. The structure of this natural eudesmane-4,11-diol has been revised from **2** to **3** (7βH-eudesmane-4α,11-diol) as a result of the analysis of the ^{1}H- and ^{13}C-nmr spectra of related natural and unnatural eudesmane derivatives.

The number of naturally occurring eudesmanes based on a cis-fused decalin system is quite limited. Occidentalol (2), chamaecynone (3), and related acetylenic norsesquiterpenes (4,5), which belong to this class of compounds, show interesting stereochemical behavior (6,7) and biological activity (8).

In 1982, Naya *et al.* isolated three *cis*-eudesmane derivatives, 5βH-eudesma-3,11-diene [**1**], 5βH-eudesma-4(14),11-diene, and amiteol from termite defense substances (9) (Figure 1). Because of the limited amount of compound isolated, the structure of **1** was elucidated based on ^{1}H-nmr spectroscopy but its stereostructure was not established clearly (9).

Recently, a new eudesmane-4,11-diol [**A**], the so-called 4,5-*epi*-cryptomeridiol was

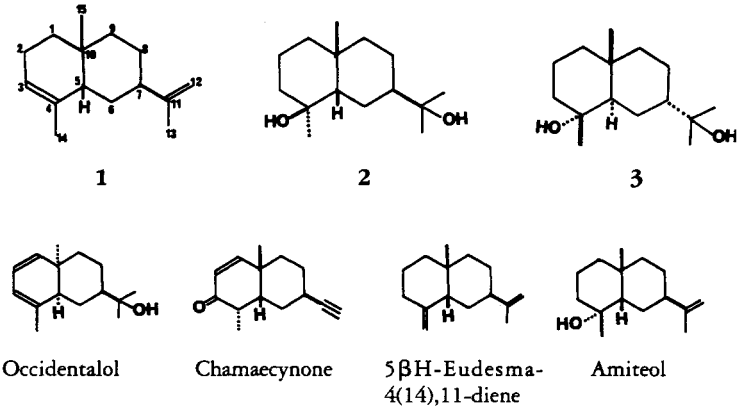


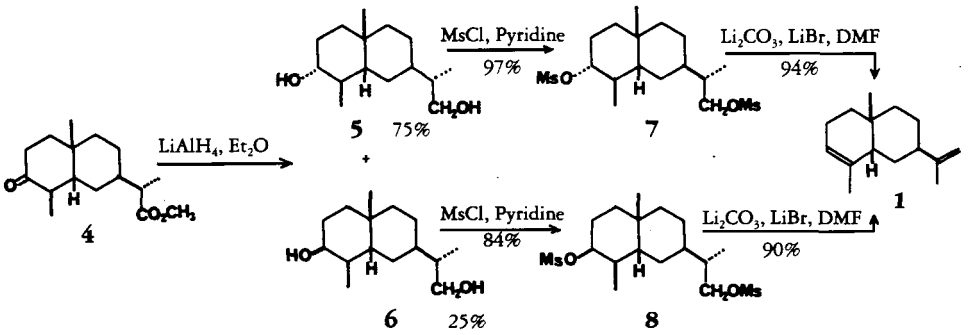
FIGURE 1. The naturally occurring eudesmanes with a cis-fused decalin system.

[1]For part 3, see Ando *et al.* (1).

isolated from a Pakistani medicinal plant, *Pluchea arguta* Boiss. (Asteraceae) by Ahmad *et al.* (10), and the structure was proposed as **2** on the basis of spectroscopic studies. Herein we report the syntheses of **1** [(+)-5βH-eudesma-3,11-diene], **2** [(−)-5βH-eudesmane-4β,11-diol], and its C-4 epimer **15** [(+)-5βH-eudesmane-4α,11-diol] by an unambiguous procedure to confirm the structure of these natural 5βH-eudesmanes. Since the ^{1}H- and ^{13}C-nmr spectra of synthetic **2** and its C-4 epimer **15** were apparently different from those of natural eudesmane-4,11-diol reported by Ahmad *et al.* (10), we discuss the stereostructure of this natural product.

RESULTS AND DISCUSSION

The synthesis commenced with methyl ester **4** prepared as previously described from α-santonin (7). Reduction of **4** with $LiAlH_4$ in Et_2O gave the 3α,12-diol **5** and the 3β,12-diol **6** in 75% and 25% yields, respectively (Scheme 1).



SCHEME 1. Synthesis of 5βH-eudesma-3,11-diene [**1**].

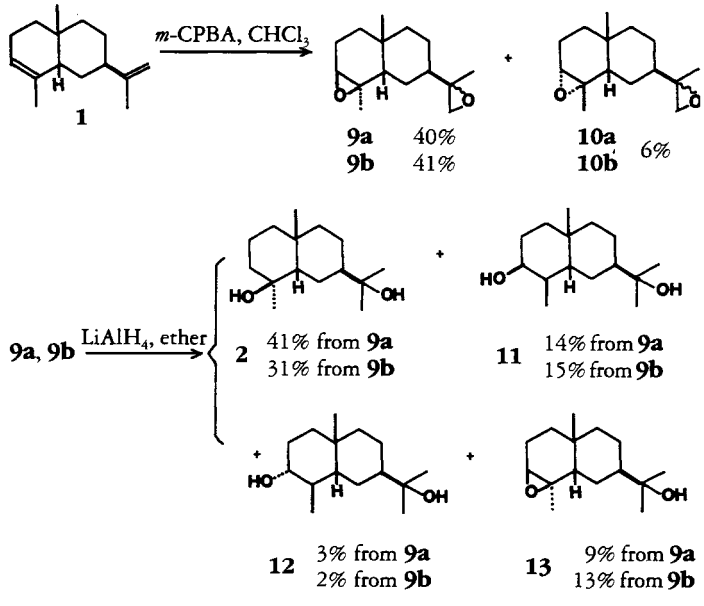
Mesylation of **5** with methanesulfonyl chloride and pyridine, and successive treatment of the resulting mesylate **7** with a mixture of LiBr and Li_2CO_3 in DMF at 150°, gave (+)-5βH-eudesma-3,11-diene [**1**] as the sole product in 91% overall yield. By analogy, mesylation of **6** and successive treatment of the resulting mesylate **8** under the same reaction conditions mentioned above gave **1** in 76% overall yield. It is interesting that both the 3α,11-diol **5** and the 3β,11-diol **6** gave the same regioisomer, the 3,11-diene [**1**], in excellent yields as the sole product. The ^{1}H-nmr spectral data of **1** were identical with those of the natural product reported in the literature (9). The spectral data of natural and synthetic **1** are summarized in Table 1.

Our attention turned next to the syntheses of 5βH-eudesmane-4β,11-diol [**2**] and 5βH-eudesmane-4α,11-diol [**15**]. Epoxidation of **1** with *m*-CPBA gave a mixture of four diepoxides, **9a**, **9b**, **10a**, and **10b** (Scheme 2). Separation of this mixture by prep. hplc gave **9a**, **9b**, and a mixture of **10a** and **10b** in 40%, 41%, and 6% yields, respectively. The major products **9a** and **9b** are epimeric at C-11 with the same stereochemistry at the 3,4-epoxide ring as determined from an analysis of their ^{1}H-nmr spectra. The stereochemistry of the 3,4-epoxide ring was assigned as β from a consideration of the fact that the reagent attacks the 3,4-double bond of **1** from the less hindered convexed face (β side) (Figure 2).

By analogy, the minor diepoxides **10a** and **10b** were assigned as 3,4-α epoxides that again possess different stereochemistry at C-11 because the reagent attacks the 3,4-

TABLE 1. ^{1}H-Nmr Spectral Data of Synthetic and Natural **1**, and ^{13}C-Nmr Spectral Data of Synthetic **1**.

Proton(s)	Synthetic **1**	Natural **1**
	^{1}H nmr ($CDCl_3$) 200 MHz	δ (ppm) 360 MHz
Me-10	1.00 (3H, s)	0.99 (3H, s)
Me-4	1.65 (3H, br s)	1.66 (3H, br s)
Me-11	1.73 (3H, s)	1.73 (3H, br s)
H-12	4.70 (2H, s)	4.69 (2H, br s)
H-3	5.43 (1H, br s)	5.43 (1H, br s)
Carbon	^{13}C nmr ($CDCl_3$) 50.3 MHz δ (ppm) (multiplicity determined by DEPT)	
C-13	21.14 (q)	
C-14	21.88 (q)	
	22.44 (t)	
	26.75 (t)	
C-15	27.30 (q)	
	29.16 (t)	
	30.99 (t)	
C-10	31.43 (s)	
	36.00 (t)	
	40.14 (d)	
	44.35 (d)	
	108.13 (t)	
C-3	122.78 (d)	
C-11	135.18 (s)	
C-4	150.56 (s)	



SCHEME 2. Preparation of 5βH-eudesmane-4β,11-diol [**2**].

double bond of **1** from the more hindered concave face (α side). The stereochemical assignment of epoxides **10a** and **10b** was also supported by analysis of the ^{1}H-nmr spectra of diols **2** and **15**, as described later.

Reduction of **9a** with $LiAlH_4$ in Et_2O gave four products, **2**, **11**, **12**, and **13**, in 41%, 14%, 3%, and 9% yields, respectively. Reduction of **9b** under the same conditions gave the same products (i.e., **2**, **11–13**) in 31%, 15%, 2%, and 13% yields, respectively.

Compound **2** was determined as the desired 5βH-eudesmane-4β,11-diol by interpretation of its ^{1}H- and ^{13}C-nmr spectra as well as from a consideration of the reaction pathway mentioned above. The C-4 stereochemistry of **2** also was supported by comparison of the δ value of H-7 with that of **15**, to be mentioned later. The only moderate yield of **2** may be explained by the fact that the reagent attacks at C-3 of **9a** or **9b** from the more hindered concave face (α side), representing the unfavorable equatorial attack of hydride (Figure 3).

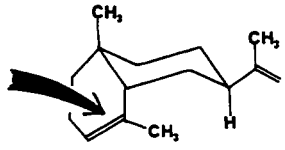


FIGURE 2. Direction of the approach of *m*-CPBA.

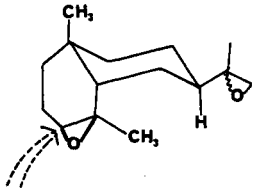
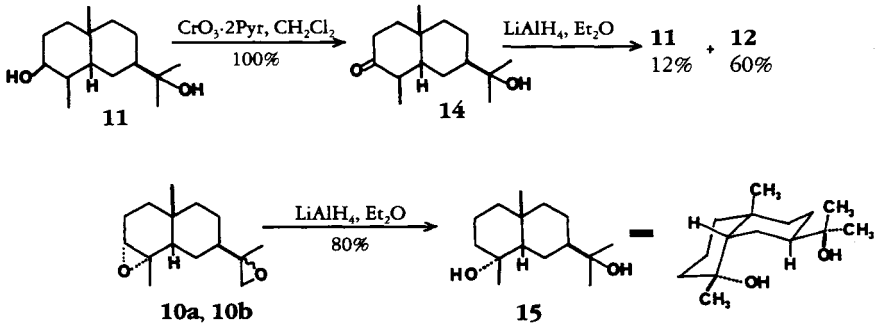


FIGURE 3. Direction of the approach of hydride.

The stereochemistry of diols **11** and **12** was determined by the *J* values of H-3 in their ^{1}H-nmr spectra and the result of the following reaction. Thus, oxidation of **11** with $CrO_3 \cdot 2Py$ in CH_2Cl_2 in pyridine and successive reduction of the resulting ketone **14** with $LiAlH_4$ gave the 3β(*ax*)-alcohol **11** and the 3α(*eq*)-alcohol **12** in 12% and 60% yields, respectively (Scheme 3).

The formation of **11** in the reduction of diepoxides **9a** and **9b** is explained by the α-axial attack of hydride toward the 3,4-β epoxide ring at C-4. The 3α-alcohol **12** may be formed by reduction of the 11,13-epoxide ring of **9a** and **9b** and successive rearrangement of the 3,4-epoxide ring of the resulting **13** to the ketone **14** followed by reduction with $LiAlH_4$. The formation of **13** in the reduction of **9a** and **9b** shows that the β-epoxide ring at the 3,4-positions of the 5βH-eudesmane derivative resists the reduction with $LiAlH_4$.



SCHEME 3. The chemical proof of stereochemistry of diols **11** and **12** by the preparation of 5βH-eudesmane-4α,11-diol [**15**] from the diepoxides **10a** and **10b**.

Reduction of a diastereomeric mixture of **10a** and **10b** with $LiAlH_4$ gave 5βH-eudesmane-4α,11-diol [**15**] as a single product in 80% yield. The high yield of **15** from **10a** and **10b** may be reasonably explained by the fact that the reagent attacked C-3 of the 3,4-epoxide ring from the less hindered convex β side by favorable axial attack. The stereochemistry of the C-4 hydroxyl group of **15** was proved to be α(*ax*) by the fact that the H-7 signal appeared at 2.10 ppm due to the deshielding effect of the syn-hydroxyl group at C-4. In contrast, the H-7 signal of **2** which possesses a β(*eq*)-OH at C-4 appeared at a higher field than 1.7 ppm, although this overlapped with other signals.

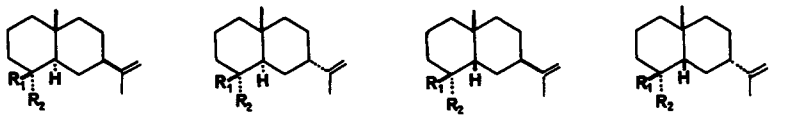
The ^{1}H- and ^{13}C-nmr spectra, as well as the physical constants of synthetic **2** and its C-4 epimer, **15**, were different from those of the natural eudesmane-4,11-diol [**A**] (Table 2). Since the stereochemistry of our synthetic **2** is correct according to the synthetic scheme mentioned above, the structure of the natural product assigned as 4,5-*epi*-cryptomeridiol must be erroneous and should be revised. Below, we discuss the correct stereostructure of this natural eudesmane-4,11-diol [**A**].

By comparison of the ^{1}H-nmr spectra of compounds **2** and **A**, a major difference was observed in the δ values of H-15 and H-14. The H-15 and H-14 signals of **2** appear at 0.13 and 0.24 ppm lower field, respectively, than those of **A**. Moreover, comparison of their ^{13}C-nmr spectra shows differences in the observed δ values of C-9, C-14, and C-15.

Recently, Wijenberg *et al.* reported the syntheses of all stereoisomers of the eudesm-11-en-4-ols **16–23**, and suggested that ^{13}C-nmr shielding data are helpful in the structure identification of similar compounds (11) (Figure 4, Table 3). Although cryptomeridiol [**26**] is a known natural eudesmane-4,11-diol (12), its C-4-epimer [**27**]

TABLE 2. Nmr Spectral Data of **2**, **15**, Cryptomeridiol [**26**], 4-*epi*-Cryptomeridiol [**27**], and Natural Eudesmane-4,11-diol [**A**] [4,5-*epi*-Cryptomeridiol as Reported in the Literature (10)].

Proton	**2**	**15**	**26**	**27**	**A**
	^{1}H nmr ($CDCl_3$) δ (ppm)				
	200 MHz	200 MHz	200 MHz	200 MHz	300 MHz
H-15	1.02	0.94	0.87	1.03	0.89
H-12	1.20	1.17	1.21	1.22	1.26
H-13	1.21	1.20	1.21	1.22	1.27
H-14	1.32	1.26	1.12	1.18	1.08
Carbon	^{13}C nmr ($CDCl_3$) δ (ppm)				
	50.3 MHz	50.3 MHz	50.3 MHz	50.3 MHz	100.64 MHz
C-1	41.45	41.73	40.99	41.44	41.47
C-2	19.91	17.42	20.15	18.12	20.28
C-3	44.06	42.59	43.43	43.85	43.65
C-4	73.25	73.26	72.32	72.10	72.65
C-5	50.72	47.61	54.76	51.71	48.84
C-6	21.41	22.00	21.47	21.40	20.69
C-7	43.27	42.99	49.89	49.99	41.98
C-8	21.46	22.25	22.51	22.46	21.40
C-9	33.10	32.38	44.57	41.57	41.65
C-10	33.76	32.74	34.50	33.66	34.34
C-11	73.93	73.58	72.95	73.03'	74.70
C-12	26.96	25.93	27.04	26.84	29.54
C-13	27.28	27.69	27.32	27.48	29.84
C-14	29.98	31.34	22.62	30.32	21.95
C-15	27.96	29.45	18.67	18.69	18.66



16 R_1=CH_3, R_2=OH **17** R_1=CH_3, R_2=OH **20** R_1=CH_3, R_2=OH **21** R_1=CH_3, R_2=OH
18 R_1=OH, R_2=CH_3 **19** R_1=OH, R_2=CH_3 **22** R_1=OH, R_2=CH_3 **23** R_1=OH, R_2=CH_3

FIGURE 4. *trans*- and *cis*-Eudesm-11-en-4-ols.

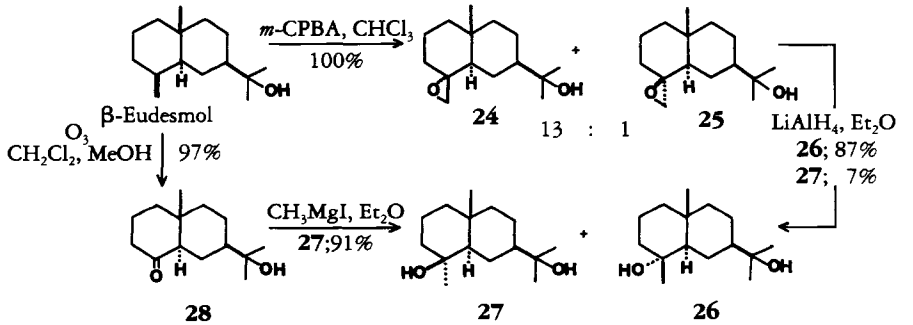
TABLE 3. Comparison of Selected ^{13}C-Nmr Spectral Data (50.3 MHz) of *trans*- and *cis*-Eudesm-11-en-4-ols (11), Natural Eudesmane-4,11-diol [**A**] (10), and Synthetic 5βH-Eudesmane-4β,11-diol [**2**].

Carbon	*trans*-eudesmanes				Natural 4,11-Diol	*cis*-Eudesmandiol				Synthetic 5βH-Eudesmane-4β,11-diol
	16	**17**	**18**	**19**	**A**	**20**	**21**	**22**	**23**	**2**
	δ (ppm) in $CDCl_3$									
C-5	54.69	49.08	51.84	45.82	48.84	47.66	53.03	49.01	51.91	50.72
C-7	46.19	39.25	46.67	39.13	41.98	39.62	45.32	39.31	45.49	43.27
C-14 ...	22.58	22.21	30.23	29.78	21.95	31.23	31.15	30.30	31.20	29.98
C-15 ...	18.61	18.38	18.66	18.31	18.66	29.49	30.50	28.91	30.65	27.96

has not yet been reported in the literature. Since the ^{1}H- and ^{13}C-nmr spectral data of cryptomeridiol [**26**] and its C-4-epimer [**27**] are needed for the purposes of comparison with those of **A**, we decided to synthesize these compounds from β-eudesmol (Scheme 4).

Epoxidation of β-eudesmol with *m*-chloroperbenzoic acid gave a 13:1 mixture of the α-epoxide **24** and the β-epoxide **25**. Reduction of this mixture with $LiAlH_4$ gave criptomeridiol [**26**] and its C-4-epimer [**27**] in 87% and 7% yields, respectively. Ozonolysis of β-eudesmol and successive reaction of the resulting nor-ketone [**28**] with MeMgI gave **27** in 88% overall yield.

In their ^{13}C-nmr spectra, the C-15 signals of the *trans*-eudesmane derivatives **16**–**19**, **26**, and **27** appeared around δ 18.5. In contrast, the C-15 signals of the *cis*-eudesmane derivatives **20**–**23** appeared around δ 28–31, as shown in Tables 2 and 3. The difference in the δ values of C-15 in these *cis*- and *trans*-eudesmane derivatives is explained by the number of gauche interactions of C-15. The C-15 signal of **2** appears at 27.96 ppm, which is in good agreement with data for other *cis*-eudesmane derivatives. In turn, the C-15 signal of the natural eudesmane-4,11-diol [**A**] appears at 18.66 ppm,



SCHEME 4. Synthesis of criptomeridiol [**26**] and its C-4-epimer [**27**] from β-eudesmol.

which is in good agreement with those of the *trans*-eudesmane derivatives. These ^{13}C-nmr spectral δ values of **2** and **A** strongly suggest that the natural eudesmane-4,11-diol [**A**] is not a *cis*- but rather a *trans*-eudesmane derivative. In eudesman-4-ols and eudesmane-4,11-diols with trans-ring fusion, the β(*ax*) C-4 Me (C-14) resonance of **16**, **17**, and **26** appears around 22.5 ppm. In contrast, the absorption of the α(*eq*) C-14 methyl group of **18**, **19**, and **27** appears around 30 ppm as indicated in Tables 2 and 3. The ^{13}C-nmr spectrum of the natural eudesmane-4,11-diol [**A**] shows a C-14 absorption at δ 21.95, which strongly suggests that the C-4 methyl and hydroxyl groups of **A** are situated in β(*ax*) and α(*eq*) fashion, respectively, in a *trans*-eudesmane skeleton.

The C-4 stereochemistry of **A** is also supported by the comparison of ^{1}H-nmr spectral data of the *trans*-eudesmane-4-ols, **16–19**, shown in Table 4 and of the *trans*-eudesmane-4,11-diols, **26** and **27**, shown in Table 2, with those of **A**. The H-15 chemical shift (δ 0.89) of **A** is in good agreement with analogous data of the *trans*-eudesman-4α-ols, **16** and **17**, and cryptomeridiol [**26**]. The H-15 signals of the *trans*-eudesman-4β-ols **18** and **19** and the *trans*-eudesmane-4β,11-diol [**27**] appeared at 0.16–0.2 ppm lower field than those of the corresponding *trans*-eudesman-4α-ols **16** and **17**, and the *trans*-eudesmane-4α,11-diol **26**, because of the deshielding effect of 4β(*ax*)-OH.

TABLE 4. Selected ^{1}H-Nmr Data (200 MHz) of *trans*-Eudesm-11-en-4-ols (11).

Compound	**16**	**17**	**18**	**19**
	δ (ppm) in $CDCl_3$			
H-15	0.83	0.90	1.03	1.06
H-13	1.68	1.72	1.71	1.71
H-14	1.06	1.06	1.12	1.13

In *trans*-eudesmane derivatives, the chemical shifts of C-5 and C-7 apparently depend on the configuration of the substituent at the C-7 position. As shown in Table 3, compounds **17** and **19** which possess an α(*ax*)-substituent at C-7 show C-5 ^{13}C-nmr absorptions at 5.61 and 6.02 ppm higher field and C-7 absorptions at 6.94 and 7.54 ppm higher field, respectively, than analogous signals of the corresponding compounds **16** and **18** possessing a β(*eq*)-substituent at C-7.

In the comparison of ^{13}C-nmr spectra of eudesmane-4α,11-diol (cryptomeridiol) [**26**], which possesses a β(*eq*)-substituent at C-7 and the natural eudesmane-4,11-diol [**A**], the δ values of **A** are in good agreement with those of the corresponding carbons of **26**, except for the absorptions of C-5 and C-7, as shown in Table 2. The C-5 and C-7 ^{13}C-nmr signals of **A** appear at 5.92 and 7.91 ppm higher field than the same signals of **26**, respectively. These observations suggest that the substituent at C-7 of **A** occurs in an α(*ax*) configuration.

In conclusion, the structure of the natural eudesmane-4,11-diol [**A**], which was isolated from *Pluchea arguta* Boiss. by Ahmad *et al.* (10), is revised from structure **2** to structure **3** (7βH-eudesmane-4α,11-diol).

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—All mps are uncorrected. ^{1}H-Nmr spectra were recorded at 200 MHz in $CDCl_3$ unless otherwise stated. ^{13}C-Nmr spectra were recorded at 50.3 MHz in $CDCl_3$. ^{13}C-Nmr assignments were determined by DEPT and CH-COSY. Mass spectra (eims and hreims) were recorded on a JEOL-HX 110 instrument. Optical rotations were determined on a Horiba Sepa-200 polarimeter in $CHCl_3$. Reactions were run under an N_2 atmosphere; Et_2O was dried over $CaCl_2$, distilled, and stored over Na wire; $CHCl_3$ was dried over $CaCl_2$ and distilled; and DMF, CH_2Cl_2, and pyridine were distilled from CaH_2. Hplc was monitored with a refractive index detector. Kieselgel 60 (Merck 70–200 mesh) was employed for column chromatography. To describe hplc conditions, column, solvent, and flow rate (ml/min)

are designated in order. The column codes are as follows: A, 250×4 mm i.d. stainless steel column packed with 10 μm Si gel; B, 250×8 mm i.d. stainless steel column packed with 10 μm Si gel; C, 300×20 mm i.d. stainless steel column packed with 15–25 μm Si gel.

METHYL (11*S*)-3-OXO-4αH,5βH-EUDESMAN-13-OATE [**4**].—A colorless oil: $[\alpha]^{25}D$ +45.1° (*c*=1.25, $CHCl_3$); ir ν max (neat) 1738, 1716 cm^{-1}; ^1H nmr δ 0.97 (3H, d, *J*=6.5 Hz, Me-4), 1.01 (3H, s, Me-10), 1.16 (3H, d, *J*=7.0 Hz, Me-11), 3.68 (3H, s, -OMe); eims *m/z* 266 (100, M^+), 179 (44), 161 (59), 123 (46), 107 (43), 88 (72); hreims *m/z* 266.18815, $C_{16}H_{26}O_3$ requires 266.18816.

(11*S*)-5βH-EUDESMANE-3α,13-DIOL [**5**] AND (11*S*)-5βH-EUDESMANE-3β,13-DIOL [**6**].—A solution of **4** (200 mg, 0.75 mmol) in Et_2O (5 ml) was slowly added into a mixture of $LiAlH_4$ (126 mg, 3.33 mmol) in Et_2O (10 ml) under stirring and then refluxed gently for 4 h. The reaction was quenched by the addition of Me_2CO (709 μl, 13.3 mmol) at 0°. The mixture was poured into saturated aqueous NaCl (10 ml), filtered through Celite under reduced pressure, and extracted with Et_2O (3×20 ml). The combined extracts were dried (Na_2SO_4), and concentrated to give a viscous oil (212 mg). On analysis of this crude product by hplc [column A, EtOAc-hexane (1:1), 2.6 ml/min] it was shown to be a 3:1 mixture of **5** (*R*, 6.4 min) and **6** (*R*, 5 min). The mixture was separated by hplc [column C, EtOAc-hexane (4:6), 15 ml/min].

The first peak (*R*, 14 min) gave **6** (43 mg, 25%) as a colorless oil: ir ν max (neat) 3368 cm^{-1}; ^1H nmr δ 0.92 (3H, d, *J*=7.0 Hz, Me-11), 0.95 (3H, d, *J*=7.0 Hz, Me-4), 0.98 (3H, s, Me-10), 3.48 (1H, dd, *J*=10.8 and 6.5 Hz, H-13), 3.63 (1H, dd, *J*=10.8 and 5.0 Hz, H-13), 3.79 (1H, br s, $W_{h/2}$=6.0 Hz, H-3); ^{13}C nmr δ 13.77 (q, C-12), 16.74 (q, C-14), 24.21 (t), 26.57 (t), 27.78 (q, C-15), 28.73 (t), 30.10 (t), 31.95 (d, C-7), 32.68 (s, C-10), 33.23 (d, C-5), 34.23 (t, C-2), 40.63 (d, C-11), 41.00 (d, C-4), 66.25 (t, C-13), 72.49 (d, C-3).

The second peak (*R*, 28 min) gave **5** (135 mg, 75%) as colorless plates: mp 93°; $[\alpha]^{25}D$ +14.9° (*c*=1.2, $CHCl_3$); ir ν max (KBr) 3276 cm^{-1}; ^1H nmr δ 0.92 (3H, d, *J*=6.8 Hz, Me-11), 0.95 (3H, s, Me-10), 0.98 (3H, d, *J*=6.3 Hz, Me-4), 3.12 (1H, ddd, *J*=10.0, 10.0, and 4.4 Hz, H-3), 3.47 (1H, dd, *J*=8.3 and 5.2 Hz, H-13), 3.64 (1H, dd, *J*=8.3 and 4.0 Hz, H-13); ^{13}C nmr δ 13.41 (q, C-12), 15.25 (q, C-14), 24.28 (t), 26.97 (t), 27.76 (q, C-15), 30.66 (t), 30.85 (t), 32.21 (d, C-7), 32.69 (s, C-10), 37.48 (d, C-5), 38.98 (t, C-2), 40.61 (d, C-11), 46.99 (d, C-4), 66.26 (t, C-13), 76.45 (d, C-3); eims *m/z* 222 (34, M^+-H_2O), 207 (32), 163 (100), 109 (42), 81 (39); hreims *m/z* 222.19837, $C_{15}H_{26}O$ (M^+-H_2O) requires 222.19834.

(11*S*)-5βH-EUDESMANE-3α,13-DIOL DIMETHANESULFONATE [**7**].—To a stirred solution of **5** (1.0 g, 4.16 mmol) in pyridine (40 ml) was added methanesulfonyl chloride (1.28 ml, 16.6 mmol) at 0°. The mixture was allowed to stand at 0° for 30 min and then at 23° for 14 h. The reaction mixture was poured into saturated aqueous NaCl (150 ml) and extracted with Et_2O (4×50 ml). The combined extracts were washed with 6 M HCl (5×40 ml) and saturated aqueous NaCl (4×30 ml), dried (Na_2SO_4), and concentrated to give **7** (1.60 g, 97%) as a colorless oil: ir ν max ($CHCl_3$) 1336, 1174 cm^{-1}; ^1H nmr δ 0.96 (3H, s, Me-10), 0.99 (3H, d, *J*=7.0 Hz, Me-11), 1.00 (3H, d, *J*=6.4 Hz, Me-4), 3.02 (6H, s, $-SO_3Me$), 4.10 (1H, dd, *J*=9.5 and 6.5 Hz, H-13), 4.19 (1H, dd, *J*=9.5 and 5.0 Hz, H-13), 4.26 (1H, ddd, *J*=11.0, 11.0, and 4.5 Hz, H-3).

PREPARATION OF 5βH-EUDESMA-3,11-DIENE [**1**] FROM **7**.—A mixture of **7** (1.57 g, 3.96 mmol), LiBr (1.37 g, 15.8 mmol), and Li_2CO_3 (1.76 g, 23.8 mmol) in DMF (50 ml) was stirred at 150° (bath temperature) for 1 h, cooled, and filtered under reduced pressure. The filtrate was poured into saturated aqueous NaCl (150 ml) and extracted with Et_2O (100 ml, 3×50 ml). The combined extracts were washed with saturated aqueous NaCl (3×100 ml), dried (Na_2SO_4), and concentrated to give a pale yellow oil (0.81 g), which was purified by column chromatography (column 3.4 cm i.d., Si gel; 41 g; solvent, hexane) to give **1** (765 mg, 94%) as a colorless oil: $[\alpha]^{25}D$ +30.1° (*c*=3.50, $CHCl_3$); ir ν max (neat) 3092, 1646, 888 cm^{-1}; ^1H nmr δ 1.00 (3H, s, Me-10), 1.65 (3H, br s, Me-4), 1.73 (3H, s, Me-11), 4.70 (2H, s, H-12), 5.43 (1H, br s, $W_{h/2}$=9.0 Hz, H-3); ^{13}C nmr δ 21.14 (q, C-13), 21.88 (q, C-14), 22.44 (t), 26.75 (t), 27.30 (q, C-15), 29.16 (t), 30.99 (t), 31.43 (s, C-10), 36.00 (t), 40.14 (d), 44.35 (d), 108.13 (t, C-12), 122.78 (d, C-3), 135.18 (s, C-11), 150.56 (s, C-4); eims *m/z* 204 (48, M^+), 161 (100), 122 (73), 109 (86), 93 (74), 91 (50); hreims *m/z* 204.18814, $C_{15}H_{24}$ requires 204.18777.

(11*S*)-5β-EUDESMANE-3β,13-DIOL DIMETHANESULFONATE [**8**].—To a stirred solution of **6** (650 mg, 2.70 mmol) in pyridine (30 ml) was added methanesulfonyl chloride (0.83 ml, 10.8 mmol). The mixture was treated in the same way as described in the preparation of **7** to give **8** (895 mg, 84%) as a colorless oil: ir ν max (neat) 1354, 1178 cm^{-1}; ^1H nmr δ 0.99 (3H, d, *J*=6.5 Hz, Me-11), 1.00 (3H, d, *J*=6.5 Hz, Me-4), 1.00 (3H, s, Me-10), 3.01 (6H, s, $-SO_2Me$), 4.09 (1H, dd, *J*=9.7 and 6.2 Hz, H-13), 4.19 (1H, dd, *J*=9.7 and 5.4 Hz, H-13), 4.83 (1H, br s, $W_{h/2}$=6.5 Hz, H-3).

PREPARATION OF **1** FROM **8**.—The dimethanesulfonate **8** (150 mg, 0.378 mmol) was treated in the same way as described in the preparation of **1** from **7** and gave **1** (69.5 mg, 90%) as a colorless oil.

EPOXIDATION OF **1** TO FORM DIEPOXIDES **9a**, **9b**, **10a**, AND **10b**.—A mixture of **1** (200 mg, 0.98 mmol) and 89% *m*-CPBA (532 mg, 2.74 mmol) in $CHCl_3$ was allowed to stand at 0° for 1 h and at 23° for 30 min. The mixture was then poured into a mixture of an aqueous solution of KI (KI 286 mg/H_2O 100 ml) and saturated aqueous NaCl (150 ml), and extracted with $CHCl_3$ (3×100 ml). The combined extracts were washed successively with 0.1 M aqueous $Na_2S_2O_3$ (3×50 ml), saturated aqueous $NaHCO_3$ (100 ml), and saturated aqueous NaCl (100 ml), dried (Na_2SO_4), and concentrated to give a colorless oil (249 mg), which was separated by hplc [column B, EtOAc-hexane (1:9), 6.0 ml/min].

The first peak (*R*, 6.3 min) gave a mixture of **10a** and **10b** (14 mg, 6%) as colorless plates: ^{1}H nmr δ 0.92 (s), 0.93 (s), 1.28 (s), 1.30 (s), 2.52 (d, *J*=4.8 Hz), 2.70 (d, *J*=4.8 Hz), 2.87 (d, *J*=4.5 Hz).

The second peak (*R*, 7.3 min) gave **9a** (92 mg, 40%) as colorless plates mp 68°: $[\alpha]^{25}D$ +0.56° (*c*=0.88, $CHCl_3$); ir ν max ($CHCl_3$) 1232, 898, 840 cm^{-1}; ^{1}H nmr δ 0.93 (3H, s, Me-10), 1.27 (3H, s, Me-4), 1.33 (3H, s, Me-11), 2.56 (1H, d, *J*=5.0 Hz, H-13), 2.62 (1H, d, *J*=5.0 Hz, H-13), 2.95 (1H, br s, $W_{h/2}$=4.0 Hz, H-3).

The third peak (*R*, 9.0 min) gave **9b** as a colorless oil (95 mg, 41%): ir ν max ($CHCl_3$) 1272, 902, 830 cm^{-1}; ^{1}H nmr δ 0.93 (3H, s, Me-10), 1.27 (3H, s, Me-4), 1.31 (3H, s, Me-11), 2.57 (1H, d, *J*=4.8 Hz, H-13), 2.62 (1H, d, *J*=4.8 Hz, H-13), 2.94 (1H, br s, $W_{h/2}$=4.0 Hz, H-3).

REDUCTION OF **9a** WITH LITHIUM ALUMINUM HYDRIDE AND PREPARATION OF 5βH-EUDESMANE-4β,11-DIOL [**2**].—A solution of **9a** (30 mg, 0.13 mmol) in Et_2O (2 ml) was slowly added into a mixture of $LiAlH_4$ (48 mg, 1.27 mmol) and Et_2O (4 ml) and stirred at room temperature. $LiAlH_4$ (48 mg) was added three times to the mixture after 7 h, 23 h, and 35 h. Stirring was continued at room temperature for 11 h after the completion of addition of $LiAlH_4$, and the reaction was quenched by addition of Me_2CO (1.08 ml, 20.3 mmol). The mixture was poured into saturated aqueous NaCl (150 ml), stirred for 30 min, filtered through Celite, and extracted with Et_2O (4×30 ml). The combined extracts were washed with saturated aqueous NaCl, dried (Na_2SO_4), and concentrated to give a colorless oil (50 mg), which was separated by hplc [column B, EtOAc-hexane (4:6), 6.0 ml/min].

The first peak (*R*, 4.2 min) gave **13** (2.8 mg, 9%) as a colorless oil: ir ν max ($CHCl_3$) 3616, 3480, 1212, 898 cm^{-1}; ^{1}H nmr δ 0.92 (3H, s, Me-10), 1.196 (3H, s, Me-11), 1.203 (3H, s, Me-11), 1.36 (3H, s, Me-4), 2.96 (1H, br s, $W_{h/2}$=4.0 Hz, H-3).

The second peak (*R*, 5.9 min) gave **11** (4.4 mg, 14%) as colorless plates, mp 175°: ir ν max (KBr) 3368 cm^{-1}, ^{1}H nmr δ 0.96 (3H, d, *J*=6.9 Hz, Me-4), 0.99 (3H, s, Me-10), 1.18 (6H, s, Me-11), 3.81 (1H, ddd, *J*=2.2, 2.2, and 2.2 Hz, H-3); eims *m/z* 222 (2, M^+-H_2O), 149 (100), 109 (90); hreims *m/z* 222.19820, $C_{15}H_{26}O$ (M^+-H_2O) requires 222.19834.

The third peak (*R*, 10.1 min) gave **12** (0.9 mg, 3%) as a colorless oil: ir ν max ($CHCl_3$) 3616, 3452 cm^{-1}; ^{1}H nmr δ 0.95 (3H, s, Me-10), 0.99 (3H, d, *J*=6.2 Hz, Me-4), 1.18 (6H, s, Me-11), 3.14 (1H, ddd, *J*=10.0, 10.0, and 4.3 Hz, H-3).

The fourth peak (*R*, 14.3 min) gave **2** (12.7 mg, 41%) as colorless plates, mp 114°; $[\alpha]^{20}D$ −41.1° (*c*=0.23, $CHCl_3$); ir ν max (KBr) 3380 cm^{-1}; ^{1}H nmr δ 1.02 (3H, s, Me-10), 1.20 (3H, s, Me-11), 1.21 (3H, s, Me-11), 1.32 (3H, s, Me-4); ^{13}C nmr δ 19.91 (t, C-2), 21.41 (t, C-6), 21.46 (t, C-8), 26.96, 27.28 (q, C-12, C-13), 27.96 (q, C-15), 29.98 (q, C-14), 33.10 (t, C-9), 33.76 (s, C-10), 41.45 (t, C-1), 43.27 (d, C-7), 44.06 (t, C-3), 50.72 (d, C-5), 73.25 (s, C-4), 73.93 (s, C-11); eims *m/z* 222 (11, M^+-H_2O), 204 (43), 164 (45), 149 (49), 109 (100), 59 (58); hreims 222.19909, $C_{15}H_{26}O$ (M^+-H_2O) requires 222.19834.

REDUCTION OF **9b** WITH LITHIUM ALUMINUM HYDRIDE.—Reduction of **9b** (27.4 mg, 0.12 mmol) with $LiAlH_4$ (132 mg, 4.64 mmol) by the analogous method used in the reduction of **9a** mentioned above gave an oily crude product (34.5 mg), which was separated by hplc [column B, EtOAc-hexane (4:6), 6.0 ml/min]. The first peak (*R*, 4.3 min) gave **13** (3.6 mg, 13%). The second peak (*R*, 6.0 min) gave **11** (4.2 mg, 15%). The third peak (*R*, 11.0 min) gave **12** (0.6 mg, 2%). The fourth peak (*R*, 15 min) gave **2** (12.7 mg, 31%).

OXIDATION OF **11** WITH CHROMIUM TRIOXIDE.—A quantity of CrO_3 (50 mg, 0.50 mmol) was added to a mixture of CH_2Cl_2 (1 ml) and pyridine (81 μl, 1.0 mmol) at 0° for 10 min. Then **11** (8.0 mg, 0.033 mmol) was dissolved in CH_2Cl_2 (1.5 ml) and added over a 5 min period, and the mixture was stirred at 0° for 2.5 h and allowed to stand at this temperature for 18 h. The reaction mixture was worked up in the usual manner to give an oily material (10.8 mg), which was chromatographed over Si gel [6 mm i.d. column, EtOAc-hexane (1:1)] to give **14** (8 mg, 100%) as a colorless oil: ir ν max (neat) 3476, 1712 cm^{-1}; ^{1}H nmr δ 1.00 (3H, d, *J*=6.5 Hz, Me-4), 1.03 (3H, s, Me-10), 1.21 (6H, s, Me-11), 2.63 (1H, dq, *J*=6.5 and 6.5 Hz, H-4).

REDUCTION OF **14** WITH LITHIUM ALUMINUM HYDRIDE.—A mixture of **14** (8.0 mg, 0.034 mmol) with $LiAlH_4$ (6.4 mg, 0.17 mmol) in Et_2O (2.5 ml) was refluxed for 2 h and poured into cold saturated aqueous NaCl (10 ml) and worked up in the usual manner to give a colorless oil (11 mg), which was separated by hplc [column B, EtOAc-hexane (4:6), 6.0 ml/min]. The first peak (*R*, 6.3 min) gave **11** (1 mg, 12%). The second peak (*R*, 10.2 min) gave **12** (4.8 mg, 60%).

REDUCTION OF A MIXTURE OF **10a** AND **10b** WITH LITHIUM ALUMINUM HYDRIDE LEADING TO THE FORMATION OF 5βH-EUDESMANE-4α,11-DIOL [**15**].—A solution of a mixture of **10a** and **10b** (12 mg, 0.05 mmol) in Et_2O (0.5 ml) was slowly added into a mixture of $LiAlH_4$ (19.3 mg, 0.51 mmol) and Et_2O (1.5 ml) at 0° and stirred for 16 h at room temperature. $LiAlH_4$ (19.3 mg, 0.51 mmol) was further added and stirring was continued for 22 h. The reaction was poured into cold saturated aqueous NaCl (50 ml) and filtered through Celite. The filtrate was worked up in the usual manner to give a colorless oil (12 mg), which was separated by hplc [column B, EtOAc-hexane (4:6), 6.0 ml/min].

The peak (*R*, 6.3 min) gave **15** (9.8 mg, 80%) as a colorless oil: $[\alpha]^{20}D$ +21.16° (*c*=0.72, $CHCl_3$); ir ν max ($CHCl_3$) 3616, 3444 cm^{-1}; ^1H nmr δ 0.94 (3H, s, Me-10), 1.17 (3H, s, Me-11), 1.20 (3H, s, Me-11), 1.26 (3H, s, Me-4), 2.00 (1H, dddd, *J*=2.0, 2.0, 4.0, and 13.0 Hz, H_{eq}-6), 2.10 (1H, dddd, *J*=4.0, 4.0, 12.0, and 12.0 Hz, H-7); ^{13}C nmr δ 17.42 (t), 22.00 (t), 22.25 (t), 25.93 (q), 27.69 (q), 29.45 (q), 31.34 (q), 32.38 (t), 32.74 (s), 41.73 (t), 42.59 (t), 42.99 (d), 47.61 (d), 73.26 (s), 73.58 (s).

4α,14-EPOXYEUDESMAN-11-OL [**24**].—A solution of β-eudesmol (500 mg, 2.25 mmol) and 78% *m*-CPBA (597 mg, 2.7 mmol) in $CHCl_3$ (25 mmol) was allowed to stand at 0° for 18 h. The mixture was poured into a mixture of 0.1 M aqueous KI (22.5 ml) and saturated aqueous NaCl (20 ml), and was extracted with $CHCl_3$ (3×30 ml). The combined extracts were washed successively with 0.1 M aqueous $Na_2S_2O_3$ (2×30 ml), saturated aqueous $NaHCO_3$ (3×30 ml), and saturated aqueous NaCl (3×30 ml), dried (Na_2SO_4), and concentrated to give a 13:1 mixture of **24** and 4β,14-epoxyeudesman-11-ol [**25**] (537 mg, 100%). A part of this mixture was recrystallized from hexane to give pure **24** as colorless crystals: mp 61°; $[\alpha]^{25}D$ −22.4° (*c*=0.84); ir ν max (KBr) 3336, 3044, 1262, 908, 826 cm^{-1}; ^1H nmr δ 0.85 (3H, s, Me-10), 1.16 (3H, s, Me-11), 1.17 (3H, s, Me-11), 2.53 (1H, d, *J*=4.5 Hz, H-14), 2.72 (1H, dd, *J*=4.5 and 2.0 Hz, H-14); ^{13}C nmr (50.3 MHz) δ 17.03 (q, C-15), 20.64 (t), 21.09 (t), 22.39 (t), 26.99 (q, C-12), 27.45 (q, C-13), 35.57 (t, C-3), 35.82 (s, C-10), 41.06 (t), 41.54 (t), 47.32 (d, C-5), 49.04 (d, C-7), 50.94 (t, C-14), 59.37 (s, C-4), 72.69 (s, C-11). *Anal.*, calcd for $C_{15}H_{26}O_2$, C 75.58, H 11.00; found C 75.28, H 10.87.

EUDESMANE-4α,11-DIOL [**26**].—To a stirred solution of $LiAlH_4$ (237 mg, 6.24 mmol) in Et_2O (16 ml) was added a 13:1 mixture of epoxides **24** and **25** (213 mg, 0.89 mmol) in Et_2O (8 ml). The solution was stirred for 7 h at 0°, poured into saturated aqueous NaCl (150 ml), and extracted with EtOAc (3×30 ml). The combined extracts were worked up as usual to give a white crystalline material, which was chromatographed over Si gel (16 g) with hexane-EtOAc (1:1).

The first fraction gave **27** (14 mg, 7%) as colorless needles. The second fraction gave spectroscopically pure **26** (186 mg, 87%), which was recrystallized from Et_2O to give colorless needles: mp 141°; $[\alpha]^{25}D$ −25.3° (*c*=1.11); ir ν max (KBr) 3396 cm^{-1}; ^1H nmr δ 0.87 (3H, s, Me-10), 1.12 (3H, s, Me-4), 1.21 (6H, s, Me-11); ^{13}C nmr δ 18.67 (q, C-15), 20.15 (t), 21.47 (t), 22.51 (t), 22.62 (q, C-14), 27.04 (q, C-12), 27.32 (q, C-13), 34.50 (s, C-10), 40.99 (t), 43.43 (t), 44.57 (t), 49.89 (d, C-7), 54.76 (d, C-5), 72.32 (s), 72.95 (s). *Anal.*, calcd for $C_{15}H_{28}O_2$, C 74.95, H 11.74; found C 74.54, H 11.88.

11-HYDROXY-14-NOREUDESMAN-4-ONE [**28**].—Ozone was bubbled into a solution of β-eudesmol (334 mg, 1.50 mmol) in a mixture of CH_2Cl_2 (16 ml) and MeOH (7.5 ml) at −70° until the solution became blue after 2.5 h. The reaction mixture was poured into a mixture of KI (623 mg, 3.75 mmol), MeOH (14 ml), and AcOH (10 ml) and stirred for 2 h. The resulting dark brown solution was poured into the stirred 0.1 M aqueous solution of $Na_2S_2O_3$ (24 ml, 2.4 mmol) and extracted with EtOAc (3×30 ml). The combined extracts were treated as usual to give spectroscopically pure **28** (326 mg, 97%) as colorless crystals, which were recrystallized from ether to give colorless cubes: mp 123°; $[\alpha]^{25}D$ +5.21° (*c*=1.23); ir ν max (KBr) 3516, 1698 cm^{-1}; ^1H nmr δ 0.77 (3H, s, Me-10), 1.19 (3H, s, Me-11), 1.21 (3H, s, Me-11); ^{13}C nmr δ 16.99 (q, C-14), 21.52 (t), 21.97 (t), 22.69 (t), 26.77 (q, C-12), 27.38 (q, C-13), 39.36 (s, C-10), 40.42 (t), 40.87 (t), 41.27 (t), 48.51 (d, C-7), 57.48 (d, C-5), 72.74 (s, C-11), 212.79 (s, C-4). *Anal.*, calcd for $C_{14}H_{24}O_2$, C 74.95, H 10.78; found C 74.70, H 10.69.

EUDESMANE-4β,11-DIOL [**27**].—Into an Et_2O solution of MeMgI prepared from Mg powder (60 mg, 2.45 mmol) and MeI (139 μl, 2.23 mmol) in Et_2O (10 ml) was added **28** (50 mg, 0.223 mmol) in Et_2O (10 ml). The solution was stirred for 2 h and poured into saturated aqueous NH_4Cl (60 ml) and extracted with Et_2O (3×20 ml). The combined extracts were worked up as usual to give spectroscopically pure **27** (59 mg, 91%), which was recrystallized from hexane to give colorless needles: mp 85°; $[\alpha]^{25}D$ +26.1° (*c*=0.82); ir ν max (KBr) 3348 cm^{-1}; ^1H nmr δ 1.03 (3H, s, Me-10), 1.18 (3H, s, Me-4), 1.22 (6H, s, Me-11); ^{13}C nmr δ 18.12 (t), 18.69 (q, C-15), 21.40 (t), 22.46 (t), 26.84 (q, C-12), 27.48 (q, C-13), 30.32 (q, C-14), 33.66 (s, C-10), 41.44 (t), 41.57 (t), 43.85 (t), 49.99 (d, C-7), 51.71 (d, C-5), 72.10 (s), 73.03 (s). *Anal.*, calcd for $C_{15}H_{28}O_2$, C 74.95, H 11.74; found C 74.56, H 11.93.

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