Rearrangements of the C/D Ring System of the Tetracyclic Diterpenoid, Aphidicolin

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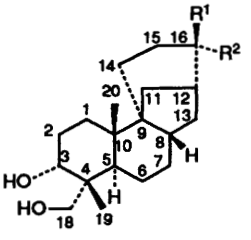
The generation of a C-16 carbocation in the aphidicolane series by the hydrolysis of a 15β,16β- or a 16β,17-epoxide is shown to lead, *inter alia*, to skeletal rearrangement products arising from the migration of the C(12)–C(13) bond to C-16.

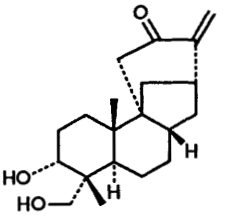
The bridged C/D ring systems of the tetracyclic diterpenoids undergo a number of skeletal rearrangements. Those linking the kaurene, beyerene and the atiserene skeleta have been examined on a number of occasions particularly in the context of their biogenesis.[1] A comparable series of diterpenoid skeleta are now known in which one terminus of the bridge is at C-9 rather than C-8. These are exemplified by aphidicolin **1**.[2] Rings C and D of



1 R^1 = OH, R^2 = CH_2OH
2 R^1, R^2 =
3 R^1 = CH_2OH, R^2 = OH

aphidicolin **1** form a bicyclo[3.2.1]octane. This type of ring system is known to undergo a variety of skeletal rearrangements.[3–5] Some rearrangements of related tetracyclic ring systems have already been examined in the course of the total syntheses of aphidicolin and diterpenoids of the stemodin–maritimol series.[6] In this paper we report some skeletal rearrangements arising from the formation of a C-16 carbocation. These may have some implications as far as the relationships between the naturally occurring compounds of these series are concerned.

Whilst preparing some derivatives of aphidicolin **1** for biological investigation, we attempted a partial synthesis of the unsaturated ketone **4** by oxidation of the 15β,16β-epoxide **6** with chromium trioxide[7] to a 15,16-ketol to be followed by dehydration. Instead of the desired product, the oxidation led to skeletal rearrangements. Thus, oxidation of the acetonide **6** of 15β,16-epoxyaphidicolane-3α,18-diol[8] with chromium trioxide at −10 °C, gave two products, the first product **9** of which retained the acetonide and contained two carbonyl groups (ν_{max}/cm^{-1} 1710 and 1740; δ_C 208.3 and 209.4). This product could also be obtained by separate acid hydrolysis and oxidation. Thus, hydrolysis of the epoxide **5** with acid gave a tetraol **7** which only formed a monoacetonide **8**. Oxidation of the remaining free hydroxy groups then gave the diketone **9**. The second product from the oxidation of the epoxide **6** was a ketol **10** (ν_{max}/cm^{-1} 3440 and 1730; δ_C 70.2 and 217.9). However dehydration of this ketol with methanesulfonyl chloride gave a trisubstituted alkene **11** [δ_H 5.11 ($W_{\frac{1}{2}}$6 Hz)] with a methyl group on the double bond (δ_H 1.65). The alkene



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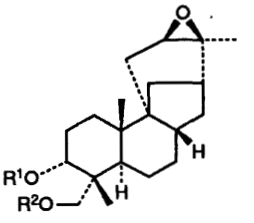
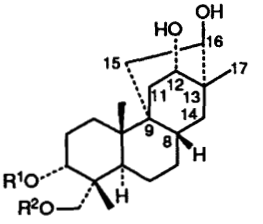
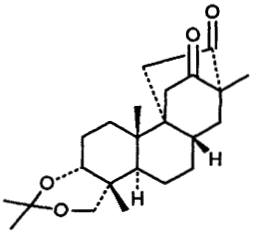


5 R^1 = R^2 = H
6 R^1, R^2 =



7 R^1 = R^2 = H
8 R^1, R^2 =

was not conjugated with the ketone. Neither sets of functional groups could be readily accommodated on the unrearranged aphidicolane skeleton. There were, however, plausible rearrangement products based on the formation of a C-16 carbocation. Although many of the compounds in this series were gums, the diketone **9** and the unsaturated ketone **11** were



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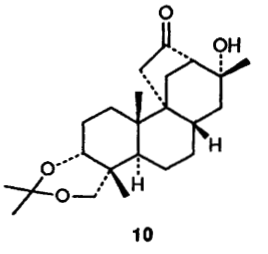

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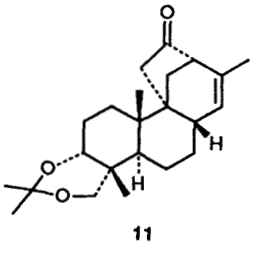

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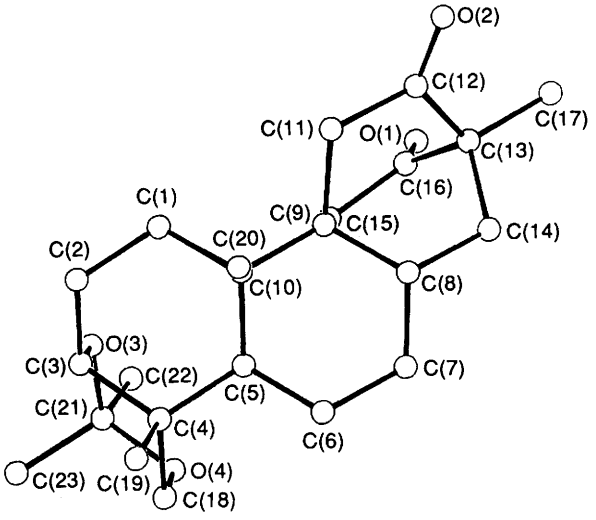


Fig. 1 X-ray molecular structure of compound **9**

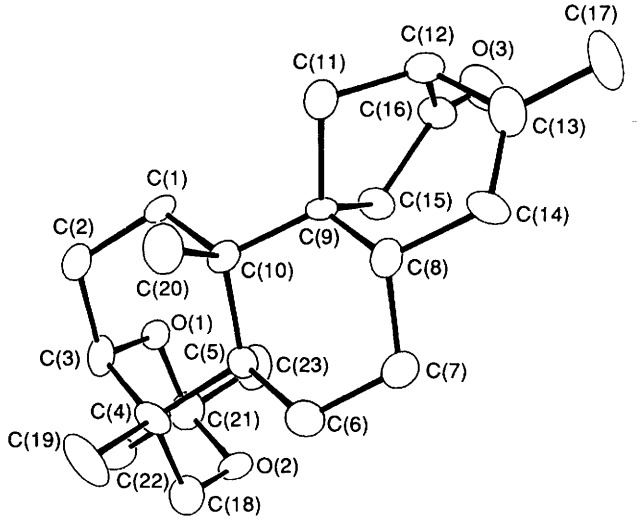
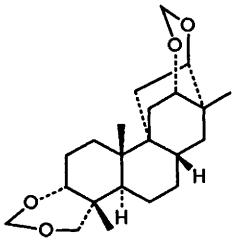


Fig. 2 X-ray molecular structure of compound **11**

both crystalline and hence their structures were confirmed by X-ray crystallography (see Figs. 1 and 2).*

This left the stereochemistry of the hydroxy groups in compound **7** to be determined. Although the tetraol **7** did not form a bisacetonide, on treatment with methoxyethoxymethyl chloride (MEMCl) followed by reaction with zinc bromide, it formed a bismethylene ether **12** thus linking the ring D hydroxy



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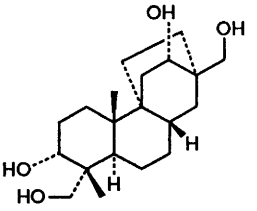
groups and defining their stereochemistry as 12α,16β. Inspection of molecular models shows that there would be severe steric crowding between the methyl groups of an acetonide and the remainder of the C/D ring system (*e.g.* 15-H) accounting for the difficulty in the formation of this derivative. The stereochemistry of the hydroxy group in compound **10** was tentatively assigned on the basis of the probable participation of the chromate ester in its formation (see Scheme 1).

The formation of a carbocation at C-16 plays a central role in these rearrangement reactions. Such a carbocation may also be generated by the fission of a 16β,17-epoxide **2**. This reaction has been described previously[2] but only the isolation of the 16-epimers of aphidicolin, **1** and **3**, was reported. Further examination of the reaction revealed the presence of a tetraol **13**. The NMR spectra of this product contained signals δ_H 3.61 and 3.78; δ_C 71.4 and δ_H 3.87 and δ_C 75.8, (C-18 and C-3 respectively) assigned by comparison with aphidicolin **1**. The ^{1}H NMR spectrum contained a second set of AB-doublets (δ_H 3.72 and 3.81, 17-H_2) and a broad doublet at δ 4.28 (J 9 Hz, 12-H). Irradiation of the signal at δ 4.28 gave nuclear Overhauser enhancements of two multiplets (δ 1.71 and 1.91). Irradiation of the 10-methyl signal (δ 0.95) also gave NOE enhancements of these signals. Hence these sets of protons must lie on the same face of the molecule. This confirmed the location and the stereochemistry of the 12α-hydroxy group.



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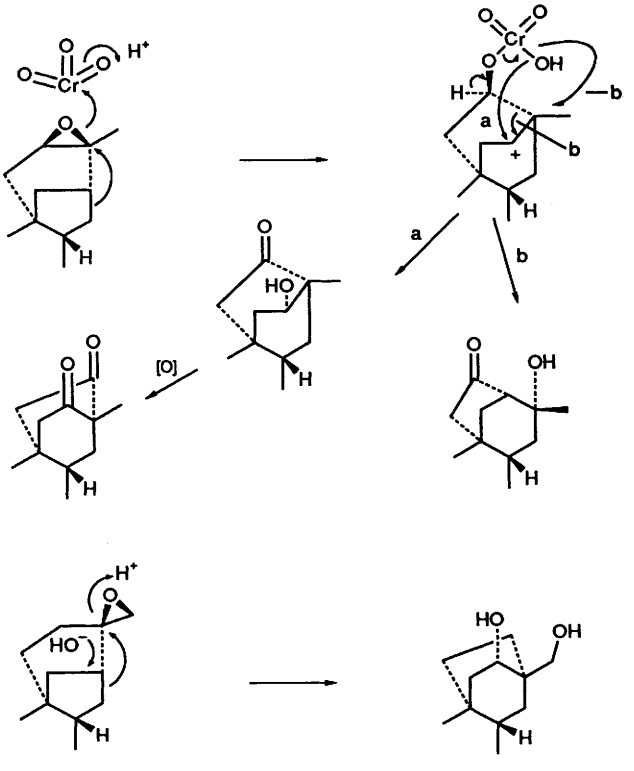
The origin of these rearrangement products may be rationalised in the terms of the initial formation of a C-16 carbocation which is then discharged by the migration of the C(13)–C(12) bond to C-16 and the attack of a nucleophile at C-12 (see Scheme 1). Alternatively, the migration of the

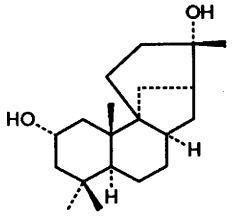


Scheme 1

* Following literature precedents[9] for related compounds, the rearrangement products are numbered as substituted podocarpanes.

C(15)–C(16) bond to C-12 then returns the carbocation to C-16 where it is again discharged by the attack of a nucleophile.

These rearrangements are of interest in view of the isolation of a number of related diterpenoids from higher plants. The formation of compound **10** mirrors the stemodin **14**–stemarin **15**[10] pair although the overall ring C/D stereochemistry is different from that of aphidicolin (*cf.* kaurene and phyllocladene). A similar situation involves the helifulvane and villanovane diterpenoids[11] (*cf.* the trachylobane and atiserenes).



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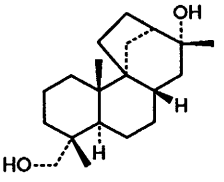

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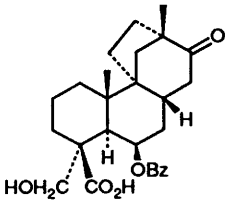

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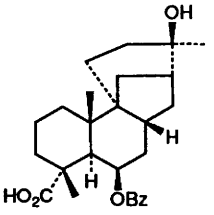

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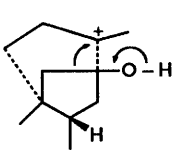
The formation of scopadulcic acid **16**[12] must also involve a C-16 carbocation and a rearrangement. However, the stereochemistry of the hydroxy group in the recently isolated scopadulin **17**[13] would not favour a concerted rearrangement to generate the skeleton of **16**. The relationship **18**–**19** may have a closer analogy to that of steviol and isosteviol.



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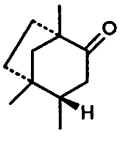

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Experimental

General Experimental Details.—^{1}H and ^{13}C NMR spectra were determined at 360 and 90.55 MHz respectively on a Bruker WM360 spectrometer for solutions in deuteriochloroform except where otherwise stated (*J*-values in Hz) ^{12}C NMR data are shown in Table 1. IR spectra were determined as Nujol mulls. Solutions were dried over sodium sulfate. Light petroleum refers to the fraction, b.p. 60–80 °C. Silica for chromatography was Merck 9385.

Oxidation of 3α,18-*Isopropylidenedioxy*-15β,16β-*epoxyaphidicolane* **6**.—A solution of chromium trioxide (3 mol dm^{-3} in sulfuric acid; 1 cm^3) was added dropwise to a stirred solution of the epoxide **6**[8] (345 mg) in acetone (7 cm^3) at −10 °C. After 10 min aqueous sodium hydrogen carbonate (50 cm^3) was cautiously added and the products were extracted with ethyl acetate. The extract was washed with aqueous sodium hydrogen carbonate and brine, dried and evaporated to give a gum which was chromatographed on silica. Elution with ethyl acetate–light petroleum (3:7) gave the 3α,18-acetonide **9** (92 mg) of 3α,18-dihydroxy-13-methyl-9α,13α-ethanopodocarpane-12,16-dione which crystallised from methanol–chloroform as needles, m.p. 157–159 °C (Found: C, 73.85; H, 9.15. $C_{23}H_{34}O_4$ requires C, 73.75; H, 9.15%); ν_{max}/cm^{-1} 1710 and 1740; δ_H 0.77 (3 H, s, 19-H), 1.09 and 1.11 (each 3 H, s, 17-H and 20-H), 1.43 and 1.44 (each 3 H, s, O_2CMe_2), 3.29 and 3.63 (each 1 H, d, *J* 12, 18-H) and 3.68 (1 H, t, *J* 3, 3-H). Further elution gave the 3α,18-acetonide **10** (55 mg) of 3α,13α,18-trihydroxy-13β-methyl-9α,12α-ethanopodocarpan-16-one as a gum; ν_{max}/cm^{-1} 1730 and 3440; δ_H 0.70 (3 H, s, 19-H), 1.12 (3 H, s, 20-H), 1,23 (3 H, s, 17-H), 1.37 and 1.38 (each 3 H, s, O_2CMe_2), 3.22 and 3.55 (each 1 H, d, *J* 12, 18-H) and 3.63 (1 H, t, *J* 2, 3-H).

Table 1 ^{13}C NMR data for the rearrangement products

	δ				
	8[a]	**9**[a]	**10**[a]	**12**[a]	**13**[b]
1	32.6	31.8	30.1	31.1	33.4
2	25.6	25.9	25.0	24.5	25.7
3	72.8	72.5	73.0	80.2	75.8
4	34.8	34.7	34.6	31.5	40.7
5	33.7	33.5	34.0	33.9	34.0
6	23.7	23.5	23.5	23.8	23.6
7	21.3	20.9	20.8	21.1	21.7
8	32.7	33.0	35.9	33.5	33.3
9	36.0	44.0	49.7	35.5	37.1
10	38.1	38.0	37.9	38.1	39.9
11	39.6	44.6	30.3	31.8	38.9
12	75.1	208.3	59.3	73.7	71.7
13	40.4	62.0	70.2	39.0	38.8
14	38.7	39.0	38.5	37.9	36.3
15	34.3	40.5	42.4	26.0	22.3
16	75.2	209.4	217.9	73.9	26.8
17	20.5	11.8	28.2	21.8	69.7
18	68.5	68.2	67.9	75.1	71.4
19	17.9	17.8	17.5	17.9	18.5
20	16.5	16.5	16.5	16.5	16.3
acetonide/methylenedioxy	98.0	98.2	97.9	79.3	
	19.1	19.0	18.9	94.0	
	29.5	29.7	29.7		

[a] Determined in $CDCl_3$. [b] Determined in C_5D_5N.

Reaction of the Ketol **10** *with Methanesulfonyl Chloride.*—Methanesulfonyl chloride (0.3 cm^3) was added to the ketol **10** (40 mg) in pyridine (0.5 cm^3) and the sealed mixture was left at room temperature for 24 h. The mixture was poured into water (30 cm^3), acidified with dil, hydrochloric acid and extracted with ethyl acetate. The extract was washed with aqueous sodium hydrogen carbonate and brine, dried and evaporated. The residue was then chromatographed on silica. Elution with ethyl acetate–light petroleum (1:9) gave the 3α,18-acetonide **11** (28 mg) of 3α,18-dihydroxy-13-methyl-9α,12α-ethanopodocarp-13-en-16-one which crystallised from ethyl acetate as prisms, m.p. 180–185 °C (Found: C, 76.7; H, 9.5. $C_{23}H_{34}O_3$ requires C, 77.05; H, 9.55%); ν_{max}/cm^{-1} 1730 and 1190; δ_H 0.67 (3 H, s, 19-H), 1.04 (3 H, s, 20-H), 1.37 and 1.38 (each 3 H, s, O_2CMe_2), 1.65 (3 H, br s, $W_{\frac{1}{2}}$ 4 Hz, 17-H), 3.30 and 3.66 (each 1 H, d, *J* 12, 18-H), 3.63 (1 H, br t, $W_{\frac{1}{2}}$ 7 Hz, 3-H) and 5.11 (1 H, m, $W_{\frac{1}{2}}$ 6 Hz, 14-H).

Hydrolysis of 15β,16-*Epoxyaphidicolane*-3α,18-*diol* **5**.—A solution of the epoxide **5** (180 mg) in dioxane (20 cm^3) was stirred with water (10 cm^3) containing toluene-*p*-sulfonic acid (10 mg) at room temperature for 1 h. The solution was

Table 2 Crystal data and structure refinement details

	9	**11**
Formula	$C_{23}H_{34}O_4$	$C_{23}H_{34}O_3$
M	374.5	358.5
Crystal size (mm)	0.3 × 0.3 × 0.3	0.3 × 0.3 × 0.3
Crystal system	Triclinic	Orthorhombic
Space group	P_1	$P2_12_12_1$
a, *b*, *c*, (Å)	9.460(2), 10.685(3), 10.915(4)	10.450(3), 13.800(2), 13,906(4)
α, β, γ (°)	75.37(3), 75.17(2), 88.25(2)	
V/Å^3	1031.2	2005.4
Z, D_c/g cm^{-3}, *F*(000)	2, 1.21, 408	4, 1.19, 784
μ (Mo − Kα)/cm^{-1}	0.8	0.7
Total unique reflections	3617	2043
Significant reflections	2524	1150
Abs. corr.	No. corr.	No corr.
Hydrogen atoms	Fixed	Fixed
R	0.050	0.100
R′	0.055	0.130

Table 3 Fractional atomic coordinates (× 10^4) for compound **9** (estimated standard deviations)

	Molecule 1			Molecule 2		
	x	*y*	*z*	*x*	*y*	*z*
O(1)	1 826	6 974	6 835	8 196(5)	3 002(5)	3 190(5)
O(2)	3 537(6)	4 568(6)	9 737(5)	6 726(6)	2 470(6)	44(5)
O(3)	7 348(5)	7 601(4)	2 408(4)	2 648(5)	1 132(4)	7 444(4)
O(4)	7 246(5)	9 818(4)	2 299(4)	2 548(5)	3 232(4)	7 740(4)
C(1)	7 226(7)	5 910(6)	4 864(6)	2 912(7)	925(6)	4 862(6)
C(2)	8 558(7)	6 116(6)	3 691(7)	1 578(7)	447(6)	5 997(6)
C(3)	8 669(7)	7 452(6)	2 828(7)	1 346(7)	1 266(6)	6 970(6)
C(4)	8 789(7)	8 501(6)	3 587(6)	1 126(7)	2 690(6)	6 340(6)
C(5)	7 556(6)	8 268(6)	4 862(6)	2 390(6)	3 204(6)	5 115(6)
C(6)	7 657(7)	9 182(6)	5 725(7)	2 252(7)	4 614(6)	4 383(6)
C(7)	6 249(8)	9 139(6)	6 769(7)	3 709(8)	5 153(6)	3 468(7)
C(8)	5 712(7)	7 791(6)	7 589(6)	4 309(7)	4 342(6)	2 487(6)
C(9)	5 724(7)	6 795(6)	6 747(6)	4 342(6)	2 881(6)	3 152(6)
C(10)	7 242(6)	6 845(6)	5 732(6)	2 817(6)	2 348(6)	4 110(5)
C(11)	5 334(8)	5 456(7)	7 706(7)	4 790(7)	2 217(6)	2 015(6)
C(12)	3 956(8)	5 448(7)	8 768(7)	6 232(7)	2 767(7)	1 059(6)
C(13)	3 108(8)	6 706(7)	8 505(7)	6 968(7)	3 768(7)	1 492(7)
C(14)	4 169(8)	7 805(7)	8 497(7)	5 864(8)	4 853(7)	1 618(7)
C(15)	4 426(7)	7 122(7)	6 098(6)	5 616(7)	2 666(7)	3 827(6)
C(16)	2 968(7)	6 932(6)	7 107(7)	7 059(7)	3 134(6)	2 868(6)
C(17)	1 626(10)	6 655(10)	9 513(10)	8 447(9)	4 285(9)	555(8)
C(18)	8 583(8)	9 801(6)	2 659(7)	1 199(8)	3 425(7)	7 388(7)
C(19)	10 387(8)	8 553(8)	3 732(8)	−442(7)	2 849(7)	6 154(7)
C(20)	8 435(7)	6 390(7)	6 483(7)	1 681(7)	2 376(7)	3 302(6)
C(21)	7 131(9)	8 848(7)	1 625(7)	2 767(8)	1 932(7)	8 301(6)
C(22)	5 525(9)	8 815(8)	1 566(8)	4 376(9)	1 856(7)	8 334(7)
C(23)	8 196(13)	9 138(9)	213(8)	1 754(11)	1 426(9)	9 673(8)

concentrated under reduced pressure and the products were recovered in ethyl acetate. The extract was washed with aqueous sodium hydrogen carbonate and brine, dried and evaporated. The residue was chromatographed on silica. Elution with ethyl acetate gave 13-methyl-9α,13α-ethanopodocarpane-3α,12α,16β,18-tetraol **7** (120 mg) as a gum ($M^+ - H_2O$, 320.234. *M* − H_2O, 320.235), ν_{max}/cm^{-1} 3330 and 1030; δ_H 0.66 (3 H, s, 19-H), 0.94 and 1.05 (each 3 H, s, 20- and 17-H), 3.32 (1 H, d, *J* 11, 18-H), 3.46 (1 H, d, *J* 11, 18-H) and 3.63 (3 H, br m, 3-H, 12-H and 16-H).

Acetonide **8**.—The above tetraol **7** (80 mg) in acetone (10 cm^3) and toluene-*p*-sulfonic acid (20 mg) were heated under reflux for 10 h. The reaction was followed by TLC which indicated complete conversion into the mono-acetonide after 10 min. No less polar compounds were formed over the remaining time. The solvent was evaporated and the product recovered in ethyl acetate. The extract was washed with aqueous sodium hydrogen carbonate and brine, dried and evaporated. The residue was chromatographed on silica. Elution with ethyl acetate–light petroleum (1:1) gave the 3α,18-monoacetonide of 13-methyl-9α,13α-ethanopodocarpane-3α,12α,16β,18-tetraol **8** (60 mg) as a gum; *m*/*z* (CI, NH_3), 396 (M + NH_4), 379 (M + H) and 378 (M); ν_{max}/cm^{-1} 3525, 3400 and 1093; δ_H 0.72 (3 H, s, 19-H), 0.97 and 1.06 (each 3 H, s, 17- and 20-H), 1.41 (6 H, s, O_2CMe_2), 3.24 and 3.60 (each 1 H, d, *J* 12, 18-H), 3.63 (3 H, br m, 3-H, 12-H and 16-H).

Diketone **9**.—A solution of the tetraol **7** (39 mg) in acetone (10 cm^3) containing toluene-*p*-sulfonic acid (5 mg) was heated gently for 10 min. The solution was cooled to 0 °C and a solution of chromium trioxide (3 mol dm^{-3} in sulfuric acid; 5 drops) was added. After 5 min, aqueous sodium hydrogen carbonate (30 cm^3) was added and the product was recovered with ethyl acetate. The extract was washed with aqueous sodium hydrogen carbonate and brine, dried and evaporated to

Table 4 Intramolecular distances (Å) and Angles (°) for compound **9** (estimated standard deviations)

	Molecule			Molecule	
	1	2		1	2
Bonds					
O(1)–C(16)	1.188(8)	1.208(9)	O(2)–C(12)	1.210(8)	1.205(9)
O(3)–C(3)	1.428(9)	1.443(9)	O(3)–C(21)	1.430(8)	1.442(9)
O(4)–C(18)	1.416(10)	1.418(9)	O(4)–C(21)	1.435(10)	1.401(8)
C(1)–C(2)	1.524(8)	1.520(8)	C(1)–C(10)	1.543(10)	1.547(8)
C(2)–C(3)	1.488(9)	1.510(11)	C(3)–C(4)	1.575(11)	1.535(9)
C(4)–C(5)	1.540(8)	1.539(7)	C(4)–C(18)	1.538(9)	1.559(11)
C(4)–C(19)	1.563(11)	1.546(10)	C(5)–C(6)	1.538(11)	1.536(8)
C(5)C(10)	1.567(8)	1.569(9)	C(6)–C(7)	1.508(9)	1.511(9)
C(7)–C(8)	1.515(9)	1.533(10)	C(8)–C(9)	1.569(10)	1.550(8)
C(8)–C(14)	1.543(9)	1.561(9)	C(9)–C(10)	1.566(8)	1.573(7)
C(9)–C(11)	1.536(8)	1.542(10)	C(9)–C(15)	1.557(10)	1.549(10)
C(10)–C(20)	1.556(10)	1.550(10)	C(11)–C(12)	1.505(9)	1.519(8)
C(12)–C(13)	1.546(10)	1.524(12)	C(13)–C(14)	1.565(12)	1.545(10)
C(13)–C(16)	1.522(12)	1.506(10)	C(13)–C(17)	1.537(11)	1.529(10)
C(15)–C(16)	1.511(8)	1.502(8)	C(21)–C(22)	1.539(12)	1.531(12)
C(21)–C(23)	1.572(11)	1.531(9)			
Angles					
C(3)–O(3)–C(21)	116.7(5)	116.2(5)	C(18)–(4)–C(21)	113.0(6)	113.3(5)
C(2)–C(1)–C(10)	112.6(5)	113.0(5)	C(1)–C(2)–C(3)	112.2(5)	111.4(6)
O(3)–C(3)–C(2)	105.3(5)	105.2(5)	O(3)–C(3)–C(4)	109.7(5)	111.0(5)
C(2)–C(3)–C(4)	111.7(6)	112.0(5)	C(3)–C(4)–C(5)	110.2(5)	110.0(5)
C(3)–C(4)–C(18)	105.0(6)	105.1(5)	C(3)–C(4)–C(19)	108.9(6)	109.8(5)
C(5)–C(4)–C(18)	109.5(5)	108.6(5)	C(5)–C(4)–C(19)	116.4(6)	116.6(5)
C(18)–C(4)–C(19)	106.2(5)	106.0(6)	C(4)–C(5)–C(6)	113.8(5)	114.3(5)
C(4)–C(5)–C(10)	117.6(5)	117.2(5)	C(6)–C(5)–C(10)	109.6(5)	109.7(5)
C(5)–C(6)–C(7)	111.2(6)	110.2(5)	C(6)–C(7)–C(8)	114.4(6)	111.9(6)
C(7)–C(8)–C(9)	113.2(5)	113.0(5)	C(7)–C(8)–C(14)	111.3(6)	111.2(6)
C(9)–C(8)–C(14)	109.8(6)	109.9(5)	C(8)–C(9)–C(10)	110.9(5)	111.5(5)
C(8)–C(9)–C(11)	107.1(5)	105.2(5)	C(8)–C(9)–C(15)	106.7(5)	108.7(5)
C(10)–C(9)–C(11)	112.6(5)	112.2(5)	C(10)–C(9)–C(15)	113.4(5)	113.3(5)
C(11)–C(9)–C(15)	105.8(5)	105.4(5)	C(1)–C(10)–C(5)	110.0(5)	109.1(5)
C(1)–C(10)–C(9)	110.7(5)	110.7(5)	C(1)–C(10)–C(20)	107.2(5)	107.4(5)
C(5)–C(10)–C(9)	107.9(5)	107.7(5)	C(5)–C(10)–C(20)	112.0(5)	112.8(5)
C(9)–C(10)–C(20)	109.0(5)	109.2(5)	C(9)–C(11)–C(12)	112.5(6)	112.3(6)
O(2)–C(12)–C(11)	124.8(7)	123.5(7)	O(2)–C(12)–C(13)	122.5(6)	123.3(6)
C(11)–C(12)–C(13)	112.7(5)	113.2(6)	C (12)–C(13)–C(14)	105.0(6)	105.8(6)
C(12)–C(13)–C(16)	105.9(6)	106.1(5)	C (12)–C(13)–C(17)	113.1(6)	113.1(7)
C(14)–C(13)–C(16)	106.5(5)	105.6(6)	C (14)–C(13)–C(17)	112.5(7)	112.1(6)
C(16)–C(13)–C(17)	113.1(7)	113.5(6)	C(8)–C(14)–C(13)	113.3(7)	113.3(5)
C(9)–C(15)–C(16)	111.8(5)	111.6(5)	O(1)–C(16)–C(13)	123.4(5)	123.4(5)
O(1)–C(16)–C(15)	123.3(6)	121.8(6)	C (13)–C(16)–C(15)	113.3(6)	114.8(6)
O(4)–C(18)–C(4)	112.2(5)	111.0(5)	O(3)–C(21)–O(4)	109.6(6)	110.8(5)
O(3)–C(21)–C(22)	105.3(6)	103.8(6)	O(3)–C(21)–C(23)	111.9(6)	111.6(6)
O(4)–C(21)–C(22)	106.0(6)	106.3(6)	O(4)–C(21)–C(23)	112.6(6)	112.7(6)
C(22)–C(21)–C(23)	111.0.0(7)	111.1(7)			

give the diketone **9** (25 mg) which was identical (TLC, m.p., IR) with the material described above.

Bismethylenedioxy Ether **12**.—The tetraol **7** (125 mg) was dissolved in a mixture of dichloromethane (3 cm^3) and *N,N*-diisopropylethylamine (2 cm^3). Methoxyethoxymethyl chloride (1 cm^3) was added in portions over 1 h at room temperature. The mixture was left overnight and then poured into dil. hydrochloric acid. The products were recovered in ethyl acetate. The extract was washed with aqueous sodium hydrogen carbonate and brine, dried and evaporated to give an oil which was taken up in ethyl acetate (10 cm^3) and treated with zinc bromide (100 mg) for 20 min at room temperature. The solution was then washed with aqueous sodium hydrogen carbonate, brine, dried and evaporated. The residue was chromatographed on silica. Elution with ethyl acetate–light petroleum (1:9) gave the 3α,18;12α,16β-bismethylenedioxy ether **12** (55 mg) of 13-methyl-9α,13α-ethanopodocarpane-3α,12α,16β,18-tetraol as a gum; *m/z* (CI, NH_3) 380 (M + NH_4) and 350 (380 − CH_2O); ν_{max}/cm^{-1} 1015 and 1050; δ_H 0.70 (3 H, s, 19-H), 1.02 and 1.14 (each, 3 H, s, 17- and 20-H), 2.91 and 3.92 (both 1 H, d, *J* 12, 18-H), 3.40 (1 H, t, *J* 3, 3-H), 3.65 and 3.74 (each 1 H, dt, *J* 10. 2, 12- and 16-H), 4.65 and 5.07 (each 1 H, d, *J* 5.8, O_2CH_2), 4.67 and 5.11 (each 1 H, d, *J* 6.7, O_2CH_2).

Hydrolysis of 16β,17-*Epoxyaphidicolane*-3α,18-*diol* **2**.—A solution of the epoxide **2** (530 mg) in dioxane (50 cm^3) was treated with water (25 cm^3) containing toluene-*p*-sulfonic acid (20 mg) at room temperature for 30 min. The solution was concentrated under reduced pressure and the products were recovered in ethyl acetate. The extract was washed with aqueous sodium hydrogen carbonate and brine, dried and evaporated. The residue was chromatographed on silica. Elution with ethyl acetate gave 13-hydroxymethyl-9α,13α-ethanopodocarpane-3α,12α,18-triol **13** (42 mg) which crystallised from ethyl acetate as needles, m.p. 183–184 °C (Found: C, 69.1; H, 10.2. $C_{20}H_{34}O_4 \cdot 0.5H_2O$ requires C, 69.1; H, 10.15%); ν_{max}/cm^{-1} 3350 and 1035; $\delta_H(C_5D_5N)$, 0.74 (3 H, s, 19-H), 0.95 (3 H, s, 20-H), 3.61 and 3.78 (each 1 H, d, *J* 11, 18-H), 3.72 and 3.81 (each, 1 H, d, *J* 10, 17-H), 3.87 (1 H, br s, $W_{\frac{1}{2}}$ 6 Hz, 3-H) and 4.28 (1 H,

Table 5 Fractional atomic coordinates ($\times 10^4$) for compound **11**

Atom	*x*	*y*	*z*
O(1)	698(7)	3854(5)	1530(5)
O(2)	2023(7)	4860(5)	2452(5)
O(3)	−3943(10)	6602(7)	1696(6)
C(1)	−1742(10)	3386(7)	2261(8)
C(2)	−683(12)	2683(7)	2128(8)
C(3)	602(12)	3138(7)	2307(8)
C(4)	783(11)	3609(8)	3269(7)
C(5)	−407(11)	4321(8)	3481(7)
C(6)	−384(12)	4800(9)	4453(8)
C(7)	−1353(13)	5562(9)	4563(8)
C(8)	−2730(12)	5198(8)	4279(8)
C(9)	−2696(9)	4747(7)	3290(8)
C(10)	−1784(10)	3905(8)	3254(7)
C(11)	−4108(12)	4504(9)	3062(9)
C(12)	−4691(11)	5500(9)	2905(8)
C(13)	−4720(14)	6118(9)	3817(9)
C(14)	−3709(11)	5986(9)	4434(9)
C(15)	−2437(10)	5548(8)	2525(8)
C(16)	−3774(12)	5984(8)	2285(8)
C(17)	−5659(16)	6871(10)	3930(10)
C(18)	1978(12)	4190(9)	3232(9)
C(19)	948(15)	2850(11)	4052(11)
C(20)	−2228(14)	3103(8)	3972(10)
C(21)	1869(12)	4418(9)	1566(9)
C(22)	2982(13)	3841(10)	1267(10)
C(23)	1500(16)	5249(9)	859(10)

d, *J* 9, 12-H). Further elution gave a mixture of aphidicolin and its 16-epimer (260 mg). A portion of this (120 mg) was heated gently with acetone (20 cm^3) containing toluene-*p*-sulfonic acid (5 mg) for 10 min. Examination of the integrals of the 17-H_2 ^1H NMR signals (aphidicolin bisacetonide, δ 3.54 and 3.75; 16-*epi*-aphidicolin bisacetonide, δ 3.73 and 3.85) indicated that this was a 3.5:1 mixture.

Crystal Structure Determinations.—A summary of the crystal data and structure refinement details are given in Table 2. In each case data were collected from a crystal mounted on an Enraf–Nonius CAD 4 diffractometer operating in the $\theta - 2\theta$ mode with $\Delta\theta = (0.8 + 0.35\tan\theta)°$ and a maximum scan time of 1 min and with monochromated Mo-Kα radiation (λ = 0.71069 Å). Unique reflections were measured for $2 < \theta < 25°$ and those reflections with $|F^2| > 3\sigma(F^2)$ were used in the refinement where $\sigma(F^2) = \{\sigma^2(I) + (0.04\ I)^2\}^{\frac{1}{2}}/L_p$. Structures were solved by direct methods using SHELXS-86.[14] Refinement was by full matrix least squares with non-hydrogen atoms anisotropic and weights of $w = 1/\sigma^2(F)$. Hydrogen atoms were included at calculated positions and held fixed with $U_{iso} = 1.3\ U_{eq}$ for the atom to which they are bonded. All calculations were done on a PDP 11/34 using the Enraf-Nonius SDP-Plus program package. Tables of fractional atomic coordinates and bond lengths and angles are given in Tables 3 and 4 (compound **9**) and Tables 5 and 6 (compound **11**). In compound **9** the two independent molecules show no significant differences. They are related by a non-crystallographic 2_1 screw axis parallel to *b* which does not extend to the rest of the structure. In compound **11** the diffraction was weak and only 1150 out of the 2043 reflections were used in the refinement. The high final residuals reflect the poor quality of the data.

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Table 6 Intramolecular distances (Å) and angles (°) for compound **11**

Bonds			
O(1)–C(3)	1.467(13)	O(1)–C(21)	1.451(14)
O(2)–C(18)	1.427(14)	O(2)–C(21)	1.384(14)
O(3)–C(16)	1.196(14)	C(1)–C(2)	1.48(2)
C(1)–C(10)	1.56(2)	C(2)–C(3)	1.50(2)
C(3)–C(4)	1.50(2)	C(4)–C(5)	1.61(2)
C(4)–C(18)	1.48(2)	C(4)–C(19)	1.52(2)
C(5)–C(6)	1.50(2)	C(5)–C(10)	1.58(2)
C(6)–C(7)	1.47(2)	C(7)–C(8)	1.57(2)
C(8)–C(9)	1.51(2)	C(8)–C(14)	1.51(2)
C(9)–C(10)	1.504(14)	C(9)–C(11)	1.55(2)
C(9)–C(15)	1.56(2)	C(10)–C(20)	1.56(2)
C(11)–C(12)	1.52(2)	C(12)–C(13)	1.53(2)
C(12)–C(16)	1.45(2)	C(13)–C(14)	1.37(2)
C(13)–C(17)	1.44(2)	C(15)–C(16)	1.56(2)
C(21)–C(22)	1.47(2)	C(21)–C(23)	1.56(2)
Angles			
C(3)–O(1)–C(21)	113.2(8)	C(18)–O(2)–C(21)	112.8(9)
C(2)–C(1)–C(10)	115.6(9)	C(1)–C(2)–C(3)	111.9(9)
O(1)–C(3)–C(2)	102.8(9)	O(1)–C(3)–C(4)	110.9(8)
C(2)–C(3)–C(4)	116(1)	C(3)–C(4)–C(5)	109.3(9)
C(3)–C(4)–C(18)	108.0(9)	C(3)–C(4)–C(19)	111(1)
C(5)–C(4)–C(18)	109.0(9)	C(5)–C(4)–C(19)	112.2(9)
C(18)–C(4)–C(19)	107(1)	C(4)–C(5)–C(6)	114.8(9)
C(4)–C(5)–C(10)	116.3(8)	C(6)–C(5)–C(10)	110.7(9)
C(5)–C(6)–C(7)	113(1)	C(6)–C(7)–C(8)	112(1)
C(7)–C(8)–C(9)	109.8(9)	C(7)–C(8)–C(14)	110.8(9)
C(9)–C(8)–C(14)	116(1)	C(8)–C(9)–C(10)	111.3(9)
C(8)–C(9)–C(11)	104.7(9)	C(8)–C(9)–C(15)	109.5(8)
C(10)–C(9)–C(11)	115.5(9)	C(10)–C(9)–C(15)	114.6(9)
C(11)–C(9)–C(15)	100.4(8)	C(1)–C(10)–C(5)	108.6(8)
C(1)–C(10)–C(9)	113.7(9)	C(1)–C(10)–C(20)	104.5(9)
C(5)–C(10)–C(9)	106.8(8)	C(5)–C(10)–C(20)	113.7(9)
C(9)–C(10)–C(20)	109.8(9)	C(9)–C(11)–C-12)	102.5(9)
C(11)–C(12)–C(13)	113(1)	C(11)–C(12)–C(16)	104(1)
C(13)–C(12)–C(16)	104(1)	C(12)–C(13)–C(14)	115(1)
C(12)–C(13)–C(17)	120(1)	C(14)–C(13)–C(17)	124(1)
C(8)–C(14)–C(13)	122(1)	C(9)–C(15)–C(16)	105.3(8)
O(3)–C(16)–C(12)	130(1)	O(3)–C(16)–C(15)	124(1)
C(12)–C(16)–C(15)	106.7(9)	O(2)–C(18)–C(4)	114(1)
O(1)–C(21)–O(2)	111.4(9)	O(1)–C(21)–C(22)	112(1)
O(1)–C(21)–C(23)	99(1)	O(2)–C(21)–C(22)	113(1)
O(2)–C(21)–C(23)	105.4(9)	C(22)–C(21)–C(23)	115(1)

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