Formation of 3(4→18)-*abeo*-Aphidicolenes *via* Cyclopropyl Intermediates. *X*-Ray Molecular Structure of 3(4→18)-*abeo*-17-Noraphidicol-2,18(4)-dien-16-one

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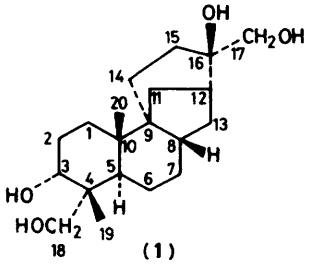
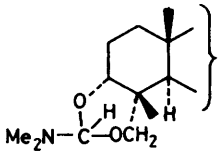
The participation of the Δ^2 double bond in the displacement of C-18 substituents on the diterpenoid aphidicolin skeleton has been shown to lead to ring expansion with the probable intervention of a cyclopropyl intermediate.

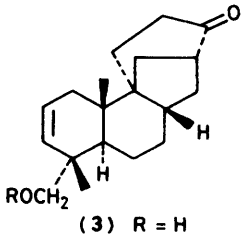
The homoallylic participation of a double bond in the substitution reactions of an alcohol and its derivatives is well documented in the steroid series.[1] In the course of biosynthetic studies[2] on the diterpenoid aphidicolin (**1**)[3] we have encountered some reactions of this type. Aphidicolin, which is of interest because of its tumour-inhibitory properties, possesses an axial 3α-hydroxy group and an equatorial hydroxymethyl group (C-18) at C-4. Interaction between these two in terms of cyclic ether, acetal, and acetonide formation has been noted previously.[3] Use can be made of this in the ready formation of the cyclic dimethylformamide acetal (**2**) and the subsequent fragmentation of its methiodide which provides an efficient route to the formate esters of 18-hydroxyaphidicol-2-enes [*e.g.* (**3**)].[4] In order to transform successfully the 18-hydroxy group into an alkyl residue, a requisite for potential biosynthetic intermediates, it was necessary first to remove the double bond. Investigation into the reasons for this revealed some ring-expansion reactions based on the participation of the Δ^2-ene in the displacement of an 18-substituent. These form the subject of this paper.



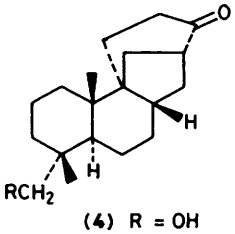
(**1**)



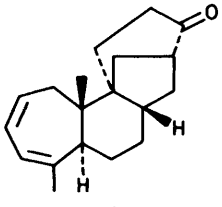
(**2**)



(**3**) R = H
(**7**) R = Ts



(**4**) R = OH
(**5**) R = Cl



Ts = *p*-$MeC_6H_4SO_2$-

(**6**)

Whereas treatment of the saturated alcohol (**4**) with triphenylphosphine and carbon tetrachloride gave the corresponding chloro compound (**5**), reaction of the unsaturated alcohol (**3**) gave a homoannular diene, $C_{19}H_{26}O$, $\lambda_{max.}$ 250 nm, ε 4 178. The ^{1}H n.m.r. spectrum showed that one of the methyl groups (δ_H 1.85) was now attached to the double bonds. The three olefinic protons comprised a complex two-proton AB system, δ_H 5.91 and 5.96 ($J_{vic.}$ 9.5 Hz) and a single-proton multiplet, δ_H 5.79, which was coupled (J 3 Hz) to the δ_H 5.91 signal. This led to the A-homodiene structure (**6**) for this product. The structure was supported by *X*-ray crystallographic analysis (see Figure).

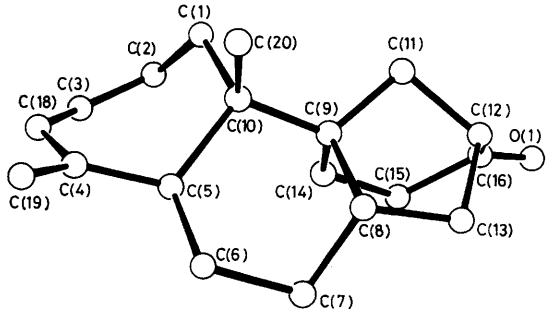
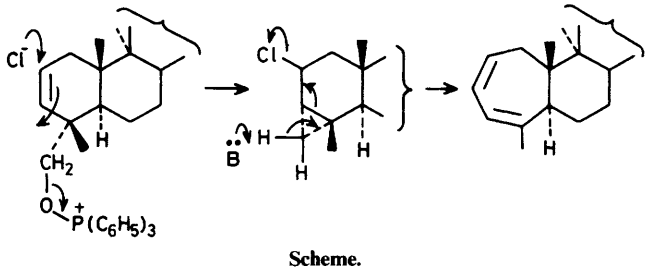


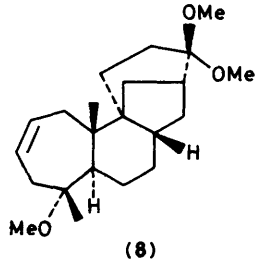
Figure. *X*-Ray molecular structure of compound (**6**)



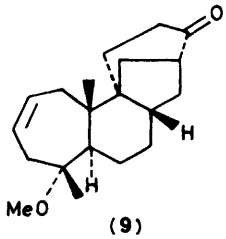
Scheme.

The mechanism of this rearrangement involves the participation of the double bond (see Scheme). The homoallylic participation of a double bond in the solvolysis of a toluene-*p*-sulphonate forms the basis of the i-steroid reaction.[1] Consequently the buffered methanolysis of the 18-toluene-*p*-sulphonate (**7**) was examined. This gave two products which were formulated as compounds (**8**) and (**9**). The former showed three methoxy resonances in the ^{1}H n.m.r. spectrum (δ_H 3.151, 3.157, and 3.166) whilst the ^{13}C n.m.r. spectrum possessed a signal at δ_C 103.34 (MeO–C(–OMe)) and no carbonyl signal. On treatment with acid, this acetal generated the second com-

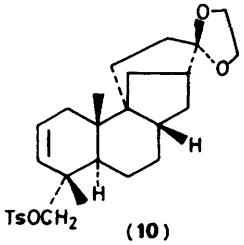
pound, (**9**). The structure of the latter was based on the following evidence. The ^{13}C n.m.r. spectrum (noise-decoupled and J.MOD) showed that it contained a tertiary methoxy group (δ_C 76.8 –C(–)–OMe; 48.1 OMe) and a disubstituted alkene (δ_C 132.1 and 127.9). The two-proton ^1H n.m.r. signal associated with this alkene formed a symmetrical multiplet at δ_H 5.79. A ^1H n.m.r. 2D COSY experiment showed that these protons were coupled to four allylic protons. The lower-field portion was coupled to signals at δ_H 2.44 ($J_{vic.}$ 7.5 Hz) and 1.96 ($J_{vic.}$ 5 Hz). These signals showed a geminal coupling of 17 Hz. The higher-field portion of the alkene signal was coupled to signals at δ_H 2.52 ($J_{vic.}$ 5 Hz) and 2.16 ($J_{vic.}$ 7.5 Hz) possessing a geminal coupling constant of 14.2 Hz. These signals did not show additional couplings and hence ring A contained the fragment –C(–)C(–)CH_2–CH=CH–CH_2C(–), thus leading to structure (**9**) for the monomethyl ether. The stereochemistry of the methoxy group followed from two sets of n.m.r. experiments. If the methoxy group were an axial substituent then it should show an n.O.e. enhancement on irradiation of both *C*-methyl groups. However, in practice it showed an n.O.e. enhancement only on irradiation of the lower-field, 19-H signal. Furthermore in an n.O.e. experiment based on irradiation of the methoxy group only the lower-field methyl group showed an n.O.e. enhancement, together with one of the allylic protons (δ_H 2.16). Secondly, examination of the undecoupled ^{13}C methyl-group signals showed that they both possessed the same long-range ^{13}C–^1H coupling pattern, *i.e.* that they both possess two ^{13}C–^1H diaxial and one axial–equatorial three-bond couplings. Hence the C-19 methyl group was assigned an axial (β) configuration and the methoxy group an equatorial (α) configuration.



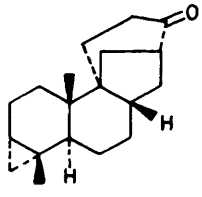
(**8**)



(**9**)



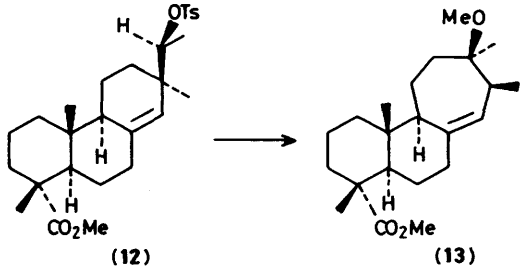
(**10**)



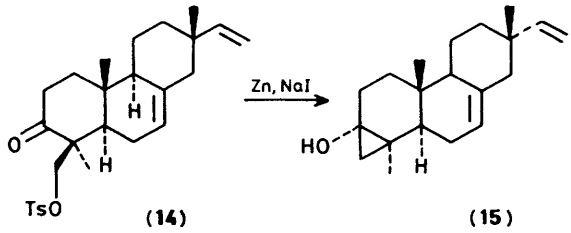
(**11**)

The mechanism of these reactions requires the formation of a cyclopropyl intermediate. We therefore examined the possibility of trapping this by a hydride reduction. The toluene-*p*-sulphonate (**7**) was converted into its 16-ethylene acetal (**10**) which was then reduced with lithium aluminium hydride in dry tetrahydrofuran (THF). This gave a complex mixture which was partially separated by chromatography. The non-polar fraction was subjected to acid hydrolysis and then rechromatographed to afford two closely related compounds, one of which was obtained pure by careful recrystallization. This compound (*m/z* 272 a.m.u.) contained proton resonances at δ_H 0.42 (dd, *J* 9 and 4 Hz) and δ_H 0.6 (dt, *J* 9 and 6 Hz) attributable to a cyclopropane ring, and two singlet methyl resonances at δ_H 0.96 and 0.99. It lacked olefinic proton resonances and was therefore assigned the structure (**11**).

These rearrangements have a number of precedents. Methanolysis of the pimar-8(14)-ene-15-toluene-*p*-sulphonates [*e.g.*, (**12**)] affords[5] the 7-membered ring of the strobanes [*e.g.*, (**13**)] whilst recently a cyclopropanol (**15**) has been identified[6] as an intermediate in the reductive rearrangement of the 19-toluene-*p*-sulphonate of virescenol C (**14**). However, in contrast to the aphidicolin system, both these examples involve axial homoallylic substituents.



(**12**) (**13**)



(**14**) (**15**)

Experimental

M.p.s were measured on a Kofler apparatus. ^1H and ^{13}C n.m.r. spectra were determined in deuteriochloroform at 360 and 90.55 MHz respectively (except where stated otherwise) on a Bruker WH 360 spectrometer. Solutions were dried over Na_2SO_4. Light petroleum refers to the fraction boiling in the range 60—80 °C.

Reaction of 18-*Hydroxy*-17-*noraphidicol*-2-*en*-16-*one* (**3**) *with Triphenylphosphine and Carbon Tetrachloride*.—A solution of 18-hydroxy-17-noraphidicol-2-en-16-one[4] (170 mg) in carbon tetrachloride (5 ml) was heated with triphenylphosphine (400 mg) and pyridine (0.5 ml) under reflux for 5 h. The products were recovered in ethyl acetate, and the solution was washed successively with dilute hydrochloric acid and water, and dried. The solvent was evaporated off to give a gum which was chromatographed on silica (light petroleum—ethyl acetate, 7:3 as eluant) to afford the A-*homo diene* (**6**), m.p. 115—120 °C (Found: C, 84.5; H, 9.6. $C_{19}H_{26}O$ requires C, 84.4; H, 9.6%); $\nu_{max.}$ 1 715 cm^{-1}; $\lambda_{max.}$ 250 nm (ε 4 178); δ_H 1.02 (3 H, s, 20-H_3), 1.85 (3 H, s, 19-H_3), and 5.79, 5.91, and 5.96 (each 1 H, m, CH=).

Crystal Structure Determination of Compound (**6**).—$C_{19}H_{26}O$, M = 270.4, orthorhombic, space group $P2_12_12_1$, a = 6.452(1), b = 8.529(6), c = 27.479(6) Å, V = 1 511.96 $Å^3$, Z = 4, D_c = 1.19 g cm^{-3}. Monochromated Mo-K_α radiation, λ = 0.710 69 Å, μ = 0.66 cm^{-1}.

Data were measured on an Enraf-Nonius CAD4 diffractometer using a crystal of dimensions *ca.* 0.38 × 0.18 × 0.20 mm. Intensities for unique data with $2 < \theta < 23°$ were measured

Table 1. Fractional atomic co-ordinates ($\times 10^4$) for compound (**6**) with estimated standard deviations in parentheses

Atom	*x*	*y*	*z*
O(1)	10 345(19)	6 278(13)	7 265(3)
C(1)	8 390(20)	−278(16)	6 630(6)
C(2)	6 393(29)	−697(16)	6 875(5)
C(3)	4 918(22)	−1 471(15)	6 655(5)
C(4)	5 550(22)	−826(16)	5 764(7)
C(5)	6 171(20)	841(14)	5 938(5)
C(6)	5 806(24)	2 007(15)	5 507(4)
C(7)	6 386(28)	3 757(17)	5 704(6)
C(8)	8 606(25)	3 728(16)	5 903(4)
C(9)	8 739(18)	2 625(13)	6 348(4)
C(10)	8 328(24)	881(14)	6 179(4)
C(11)	10 899(22)	3 014(14)	6 518(5)
C(12)	10 826(24)	4 919(16)	6 530(4)
C(13)	9 540(21)	5 305(16)	6 055(5)
C(14)	7 384(23)	3 040(16)	6 763(5)
C(15)	7 603(29)	4 592(20)	7 042(7)
C(16)	9 840(31)	5 314(16)	6 959(5)
C(18)	4 855(20)	−1 807(15)	6 137(5)
C(19)	5 454(23)	−1 303(19)	5 246(5)
C(20)	9 988(19)	352(17)	5 802(5)

using an ω–2θ scan with a maximum scan time of 2 min. No correction was made for absorption. Out of 1 399 measured, 1 281 reflections with $|F^2| > \sigma|F^2|$ were used in the refinement where $\sigma|F^2| = [\sigma^2(I) + 0.04(I)^2]^{\frac{1}{2}}/L_p$. The structure was solved by direct methods using MULTAN and refined by full-matrix least-squares with anisotropic temperature factors. No attempt was made to include hydrogen atoms. Refinement converged at $R = 0.12$, $R' = 0.16$ with a weighting factor of $\omega = 1/\sigma^2(F)$. This relatively high R value reflects the poor quality of the data since the crystal only diffracted weakly. All calculations were done on a PDP11/34 computer using the Enraf-Nonius SDP program package. Fractional atomic co-ordinates are given in Table 1 whilst the tables of intramolecular distances, bond angles, torsion angles, and anisotropic temperature factors are deposited as a Supplementary Publication SUP 56473 (4 pp.).*

18-(p-*Tolylsulphonoxy*)-17-*noraphidicol*-2-*en*-16-*one* (**7**).—A solution of 18-hydroxy-17-noraphidicol-2-en-16-one (700 mg) in pyridine (4 ml) was treated with toluene-*p*-sulphonyl chloride (500 mg) for 3 h at 0 °C. The solution was poured into ice–water and the product was recovered in ethyl acetate. The extract was washed successively with dilute hydrochloric acid, aqueous sodium hydrogen carbonate, and water, and dried. The solvent was evaporated off and the product was recrystallized from ethyl acetate–light petroleum to afford the *toluene*-p-*sulphonate* (**7**) (840 mg), m.p. 130—132 °C (Found: C, 70.4; H, 7.7. $C_{26}H_{34}O_4S$ requires C, 70.55; H, 7.7%); $\nu_{max.}$ 1 730, 1 590, 1 175, 830, and 810 cm^{-1}; δ_H 0.88 (3 H, s, 20-H_3), 1.05 (3 H, s, 19-H_3), 2.42 (3 H, s, Ar*Me*), 3.50 and 3.75 (each 1 H, d, *J* 10 Hz, together 18-H_3), 5.1 (1 H, dd, *J* 2 and 10 Hz), 5.65 (1 H, ddd, *J* 10, 5, and 2 Hz) (2-and 3-H), and 7.45 (4 H, d, *J* 8 Hz, ArH).

Methanolysis of the Toluene-p-*sulphonate* (**7**).—The toluene-*p*-sulphonate (**7**) (800 mg) was heated under reflux in methanol (20 ml) containing anhydrous sodium acetate (800 mg) for 5 h. The solvent was evaporated off under reduced pressure and the residue was chromatographed on silica. Elution with 10% ethyl acetate:light petroleum gave 4α,16,16-*trimethoxy*-3(4→18)-abeo-17-*noraphidicol*-2-*ene* (**8**) (200 mg), m.p. 108—110 °C (Found: C, 74.9; H, 10.1. $C_{22}H_{36}O_3$ requires C, 75.8; H, 10.4%); $\nu_{max.}$ 1 200 and 1 070 cm^{-1}; δ_H 0.97 (3 H, s, 20-H_3), 1.06 (3 H, s, 19-H_3), 3.151, 3.157, and 3.166 (each 3 H, s, OMe), and 5.79 (2 H, m) (for ^{13}C n.m.r. data see Table 2).

Further elution gave 4α-*methoxy*-3(4→18)-abeo-17-*noraphidicol*-2-*en*-16-*one* (**9**) (125 mg) (Found: C, 79.7; H, 9.7. $C_{20}H_{30}O_2$ requires C, 79.4; H, 9.9%); $\nu_{max.}$ 1 700 cm^{-1}; δ_H 1.04 (3 H, s, 20-H_3), 1.08 (3 H, s, 19-H_3), 3.18 (3 H, s, OMe), 5.78 (2 H, m, CH=) (for ^{13}C n.m.r. data see Table 2).

Treatment of the trimethoxyacetal (**8**) (50 mg) in THF (1 ml) with hydrochloric acid (5 drops) at room temperature for 2 h gave compound (**9**) (20 mg), identified by its ^1H n.m.r. spectrum.

Acetalization of the Toluene-p-*sulphonate* (**7**).—The toluene-*p*-sulphonate (**7**) (400 mg) was heated in benzene (20 ml) with ethylene glycol (5 ml) and toluene-*p*-sulphonic acid (200 mg) under reflux under a Dean–Stark water separator for 2 h. The product was recovered with ethyl acetate to afford the 16,16-*ethyleneacetal* of 18-(*p*-tolylsulphonyloxy)-17-noraphidicol-2-en-16-one (**10**) (377 mg), as needles, m.p. 118—120 °C (Found: C, 69.2; H, 7.8. $C_{28}H_{38}O_5S$ requires C, 69.1; H, 7.9%); $\nu_{max.}$ 1 600 cm^{-1}; δ_H (60 MHz) 0.90 (3 H, s, 20-H_3), 1.0 (3 H, s, 19-H_3), 2.45 (3 H, s, Ar*Me*), 3.6 and 3.8 (AB doublet, *J* 10 Hz), 3.95 (4 H, s, OCH_2CH_2O), 5.1 (1 H, dd, *J* 4 and 10 Hz), 5.7 (1 H, ddd, *J* 2, 6, and 10 Hz), and 7.3 and 7.8 (each 2 H, d, *J* 8 Hz, ArH).

Reduction of the Toluene-p-*sulphonate* (**10**) *with Lithium Aluminium Hydride*.—The toluene-*p*-sulphonate (**10**) (190 mg) was heated in dry THF (15 ml) under reflux with lithium aluminium hydride (500 mg) overnight. The solvent was partly evaporated off and the product was recovered in ethyl acetate. The extract was washed successively with water and dilute hydrochloric acid, dried, and evaporated to give a gum. This was chromatographed on silica with light petroleum as eluant. After work-up, the non-polar fraction (80 mg) was dissolved in ethanol (5 ml) and the solution was treated with hydrochloric acid (5 drops) at room temperature for 2 h. The product was recovered in ethyl acetate and chromatographed on silica (light petroleum as eluant) to give a mixture of two closely related (t.l.c.) compounds. Careful crystallization from ethyl acetate gave 3,18-cyclo-17-noraphidicolan-16-one (**11**), m.p. 85—87 °C (M^+, 272. $C_{19}H_{28}O$ requires *M*, 272); $\nu_{max.}$ 1 720 cm^{-1}; δ_H 0.42 (1 H, dd, *J* 4 and 9 Hz), 0.6 (dt, *J* 9 and 6 Hz), and 0.96 (3 H, s) and 0.99 (3 H, s) (19- and 20-H_3).

Table 2. ^{13}C N.m.r. signals of the methyl ethers (**8**) and (**9**)

Carbon atom	(**8**)	(**9**)	Carbon atom	(**8**)	(**9**)
1	36.5[a]	36.4[a]	12	39.9	48.7
2	127.4	127.9	13	30.8	31.9
3	132.9	132.1	14	25.6	23.9
4	77.0	76.8	15	36.7	35.4
5	48.4	48.05	16	103.3	214.7
6	24.8	24.1	18	34.5[a]	34.5[a]
7	26.6	26.3	19	20.85	20.8
8	41.0	42.1	20	16.0	16.1
9	50.4	50.6	OMe	48.0	48.1
10	41.7	42.5		47.7	
11	27.6	34.2		47.4	

[a] Assignments may be interchanged.

Acknowledgements

We thank Dr. A. G. Avent for the determination of the n.m.r.

* For details of the Supplementary Publications Scheme, see Instructions for Authors (1986), *J. Chem. Soc., Perkin Trans. 1*, 1986, issue 1. Structure factors are available from the editorial office on request.

spectra and Dr. A. H. Ratcliffe (I.C.I. Pharmaceuticals Division) for discussions.

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