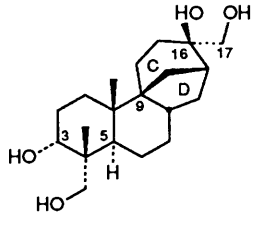
Aphidicolin Synthetic Studies: A Stereocontrolled End Game†

Carmelo J. Rizzo and Amos B. Smith, III*
Department of Chemistry, the Laboratory for Research on the Structure of Matter, and the Monell Chemical Senses Center, University of Pennsylvania, Philadelphia, Pennsylvania 19104–6323

A highly efficient, stereocontrolled synthesis of (+)-aphidicolin **1** from the well-known degradation product, acetonide 17-nor ketone **2a**, has been achieved. Key steps included palladium(0)-catalysed carbonylation of the enol triflate derived from **2a** and stereoselective epoxidation of the resultant α,β-unsaturated ester. Hydride reduction then furnished the C(16,17) vicinal diol moiety of **1**. Similarly transformed to aphidicolin were the Corey 2,2-dimethylpropylidenedioxy synthetic intermediate **2b** and the bis-*tert*-butyldimethylsilyl ether **2c**. The latter further served as synthetic precursor to the naturally occurring derivative (+)-aphidicolin 17-acetate **26**. The preparation and biological evaluation of the unnatural 16-methoxycarbonyl congeners **28** and **29** are also discussed.

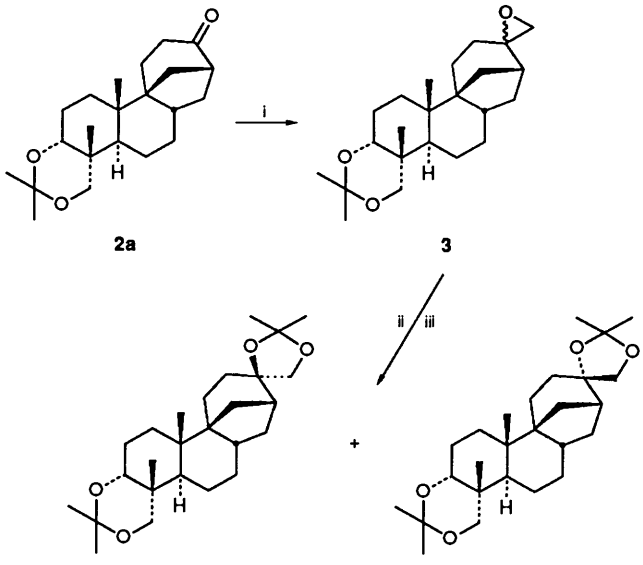
In 1972 Hesp and co-workers at ICI announced the isolation and structure of the diterpene tetraol aphidicolin **1**, produced by the fungus *Cephalosporium aphidicola*.[1] Importantly, aphidicolin proved to be active against DNA viruses[2] as well as several human and murine neoplastic cell lines,[3a] with no discernible toxicity. Later studies elucidated the mode of action, involving highly specific competitive inhibition of DNA polymerase α;[4] aphidicolin thus has no effect on non-proliferating cells. However, **1** does suffer rapid *in vivo* deactivation by liver microsomal oxidase,[3] limiting its clinical potential as an antiviral or cancer chemotherapeutic agent.



(+)-Aphidicolin **1**

The novel tetracyclic carbon skeleton of **1** incorporates eight stereocentres and a bicyclo[3.2.1]octane moiety which comprises the C and D rings. This architecture manifests a novel biosynthetic pathway involving a chair-boat folding of geranylgeranyl pyrophosphate during cyclization.[5] In conjunction with the aforementioned biological activity, the unusual structure rapidly established aphidicolin as an attractive synthetic target. Indeed, no fewer than eight total syntheses[6–13] and one formal synthesis[14] have been reported to date. Holton *et al.* recently disclosed the first enantioselective construction of **1**, unambiguously confirming the absolute stereochemistry.[12] Numerous approaches[15] to aphidicolin as well as a synthesis of the naturally occurring derivative (+)-3-deoxyaphidicolin[16] have also been described.

In analysis of the aphidicolin problem, one obvious retrosynthetic disconnection is the oxidative cleavage of the C(16,17) glycol. The ICI group thereby generated the acetonide nor ketone **2a**, which they successfully reconverted into **1**,[1b] and several published routes to aphidicolin have employed **2a** or the closely related Corey intermediate **2b**[8] as key subtargets. The Hesp conversion of **2a** into **1**[1b] involved treatment with dimethylsulphoxonium methylide, affording a mixture of epoxides **3**. Hydration with KOH followed by bisacetonide formation gave **4** and **5** in 42 and 28% overall yields. Acetonide hydrolyses then furnished aphidicolin and 16-*epi*-aphidicolin, respectively. Notably, this otherwise attractive scheme suffered from the lack of stereoselectivity in the initial epoxidation.



2a **3**

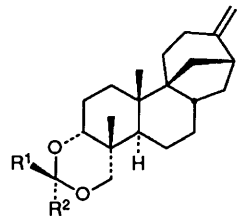
4 (42%) **5** (28%)

Reagents and conditions: i, $Me_3SO^+I^-$, NaH, DMSO; ii, KOH, H_2O, dioxane; iii, acetone, H^+

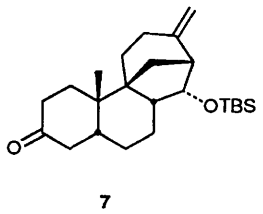
Other attempts to control the stereochemistry at C(16) have also been reported. Whereas osmylation of **6a**[7b] and **6b**[8] proved to be nonselective, Ireland and co-workers demonstrated that the homoallylic *tert*-butyldimethylsilyloxy group in **7** could be employed to direct the osmylation by blocking the α-face of the olefin.[9] Ohno utilized a similar tactic in the synthesis of 3-deoxyaphidicolin.[16] More recently, Bettolo, Lupi and Patamia showed that the introduction of two additional sp^2 centres in **8** provided enhanced conformational control in osmylation, leading to exclusive *exo* attack as well as complete regioselectivity.[11b] van Tamelen originally devised the latter approach for the synthesis of maritimol.[17]

From the outset, we regarded the development of an effective strategy for elaboration of the C-16 stereocentre as a key element of our ongoing aphidicolin program. Herein we provide a full account of experiments culminating in the stereocontrolled generation of **1** from **2a** and related 17-nor ketone precursors.[18]

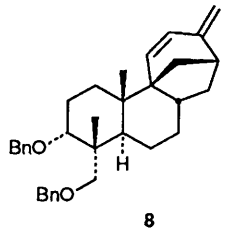
† This paper is submitted to mark the 150th anniversary of the Chemical Society/Royal Society of Chemistry.



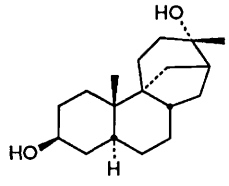
6a $R^1 = R^2 = Me$
6b $R^1 = H$, $R^2 = Bu^t$



7



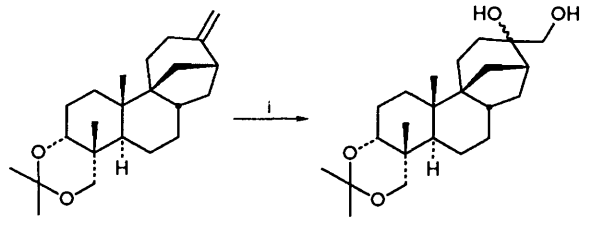
8



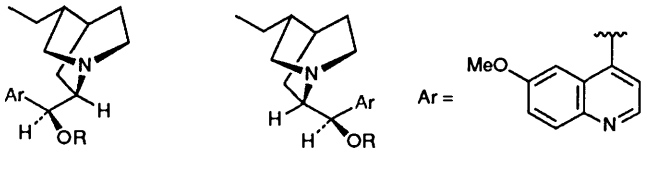
Maritimol

Reagent-controlled Approaches to C-16 *Stereoselectivity.*—Reagent-controlled enantioselective bishydroxylations and epoxidations of simple olefins have recently been reported.[19,20] Examination of molecular models suggested that double diastereodifferentiation[21] might enhance the stereoselectivity expressed in oxidation of the 16-methylene acetonide **6a** with enantiomerically pure reagents. Furthermore, antipodal reagents could lead to opposite facial selectivities, providing stereocontrolled routes to both aphidicolin and 16-*epi*-aphidicolin.

Our initial studies focused on the Sharpless asymmetric bishydroxylation protocol; this method employs cinchona alkaloids **10** and **11** as chiral ligands for osmium tetroxide.[19] Although **10** and **11** actually are diastereoisomers, they generally exert opposite directing effects in osmylation. In the event, oxidation of **6a** *via* the original Sharpless procedure afforded a 1:1 mixture of epimeric glycols **9**, as indicated by ^1H and ^{13}C NMR analysis.[22] A recently improved method,[19b] involving slow addition of the substrate and incorporation of acetate ion into the reagent system, gave similar results.



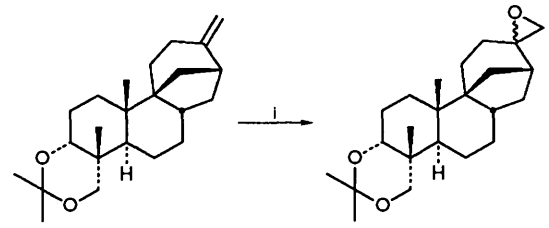
6a **9** (1:1)



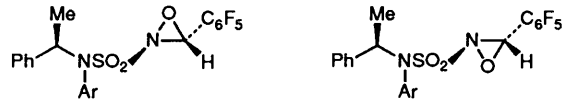
10 **11** R = *p*-Chlorobenzoyl

Reagents and conditions: i, OsO_4, **10** or **11**, NMO, $Et_4N^+OAc^-$, acetone, H_2O, 4 °C. Slow addition (12 h) of **6a** (85%).

We also investigated reagent-controlled epoxidation of **6a** with the chiral oxaziridines developed by Davis.[20] Diastereoisomers **13** and **14** were expected to furnish opposite facial selectivities in epoxidation. Unfortunately, reaction of **6a** with either **13** or **14** under the conditions reported to be optimal (CCl_4, room temp., 2 days)[20] provided a 1:1 mixture of epimeric epoxides **12**, as determined by highfield ^1H and ^{13}C NMR analysis. With the failure of the reagent control tactic, we turned our attention to substrate control.



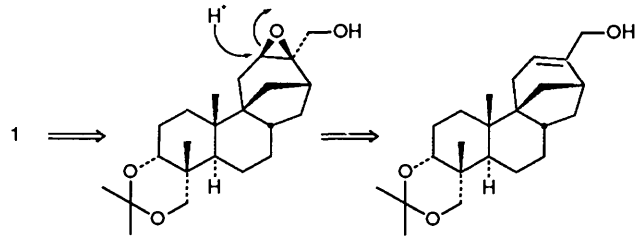
6a **12** (1:1)



13 **14**

Reagents and conditions: i, oxaziridine **13** or **14** (1 equiv.), CCl_4, room temp., 2 d (94–97%)

Substrate Control: Endocyclic Olefin Epoxidation.—At the outset of this venture, we were aware that epoxidation of bicyclo[3.2.1]oct-3-ene occurs exclusively from the *exo* face.[23] This precedent suggested that epoxidation of the allylic alcohol **16** would furnish the epoxy alcohol **15** selectively. Hydride ring opening at the less hindered position would then complete a stereocontrolled route to aphidicolin. Accordingly, we selected **16** as our initial target.

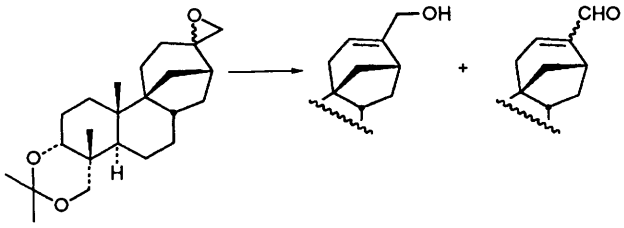


15 **16**

To this end, the Hesp mixture of the epoxides **3** was prepared; highfield NMR analysis indicated that the β:α ratio was *ca.* 2:1. Treatment of the mixture with diethylaluminium 2,2,6,6-tetramethylpiperidide[24] in benzene gave none of the desired allylic alcohol, furnishing instead a nearly 1:1 mixture of the aldehydes **17** in 75% yield (Table 1). Exposure of the epoxides to trimethylsilyl triflate[25] and DBU again produced predominantly the aldehydes **17** (83% yield). In this instance, however, a small quantity of the desired allylic alcohol **16** was also isolated. Optimal conditions (TMSOTf, CH_2Cl_2, 2,6-dimethylpyridine, −78 °C, 10 min) provided **16** in only 40% yield, together with the aldehydes (45%). In view of these difficulties, we sought an alternative approach to the epoxy alcohol **15**.

Another attractive strategy entailed conversion of a 17-nor ketone into an α,β-unsaturated ester, *via* palladium(0)-catalysed carbonylation of the corresponding enol triflate as developed by Ortar.[26] As a viable epoxidation substrate,[27] the unsaturated ester would comprise a synthetic equivalent of the allylic alcohol **16**. To test this possibility, the ketones **2a** and **2b** were quantitatively converted into the enol triflates **18a** and **18b** *via*

Table 1 Epoxide rearrangements

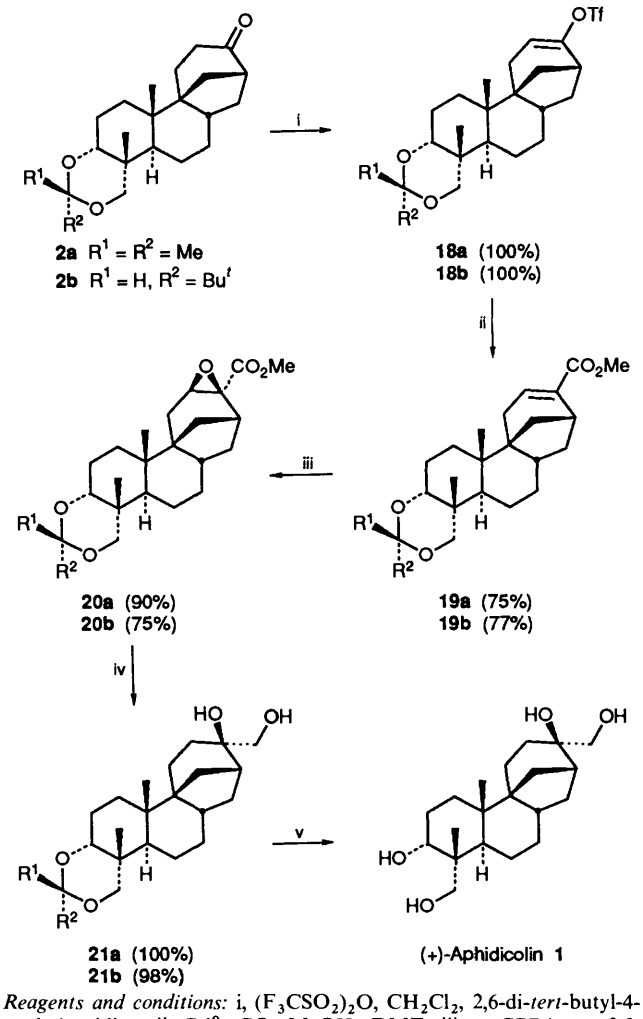


3 (2:1:1)	16 (%)	17 (%)
Et_2Al-2,2,6,6-tetramethylpiperidide, benzene, 0 °C	0	75
TMSOTf, benzene, DBU, −78 °C	11	83
TMSOTf, CH_2Cl_2, pyridine, −78 °C	30	55
TMSOTf, CH_2Cl_2, 2,6-dimethylpyridine, −78 °C	40	45

the method of Stang and Treptow.[28] Palladium(0)-catalysed carbonylation in DMF and methanol under an atmosphere of carbon monoxide[26] then furnished the corresponding α,β-unsaturated esters **19a** and **19b** in 75–80% yields. The enoate **19a** was readily epoxidized with *m*-CPBA *via* the Kishi protocol,[29] employing disodium phosphate buffer and the radical scavenger bis(2-*tert*-butyl-3-hydroxy-4-methylphenyl)-sulphide in methylene dichloride at elevated temperature. This procedure afforded the desired β-epoxy ester **20a** in 90% yield; the α-epoxide could not be detected by 500 MHz ^1H or 125 MHz ^{13}C NMR analysis. Epoxidation of **19b** under identical conditions gave the epoxy ester **20b**, again as a single stereoisomer; however, the yield was only 55%. More efficient epoxidation (*ca.* 75% yield) could be achieved by using 2,5-dinitroperoxybenzoic acid under milder conditions (CH_2Cl_2, Na_2HPO_4, bis(2-*tert*-butyl-3-hydroxy-4-methylphenyl)sulphide, room temp., 2 h).[27,30] The latter procedure furnished **20b** admixed with minor amounts of the undesired α-epoxide (15:1 ratio), as shown by highfield NMR analysis.

Reduction of the epoxy esters **20a** and **20b** with an excess of lithium aluminium hydride in THF at reflux then provided the corresponding 3α,18-protected aphidicolin derivatives **21a** and **21b** in 98–100% yields. Treatment of **20a** with only a slight excess of LAH at room temperature afforded predominantly the epoxy alcohol **15** (60% yield), derived from selective reduction of the ester moiety. Hydrolysis of **21a** was most conveniently effected with acidic ion exchange resin in methanol at reflux, generating aphidicolin almost quantitatively. Deprotection of **21b**, as described by Corey for a related compound (THF, AcOH, H_2O),[8] gave aphidicolin in 70% yield. Each sample of synthetic aphidicolin was identical in all respects, including 500 MHz ^1H and 125 MHz ^{13}C NMR, IR, MS and mixed melting point, to a sample of natural aphidicolin. The stereocontrolled, five-step conversion of **2a**, the Hesp degradation product, to aphidicolin **1** was thus accomplished in 67% overall yield, whereas the Corey intermediate **2b** furnished **1** in 40% overall yield.

Chemoselective Synthesis of Aphidicolin 17-*Acetate*.—Despite considerable promise, the usefulness of aphidicolin as a chemotherapeutic agent remains severely limited by poor water solubility as well as facile *in vivo* deactivation by oxidases.[3a,4c] In circumventing these constraints, the preparation of aphidicolin derivatives *via* chemical[31] or microbial[32] techniques may be valuable. The naturally occurring congeners 3-deoxyaphidicolin, aphidicolin 17-acetate and aphidicolin 3α,18-orthoacetate[33] have proven to be significantly less active than aphidicolin itself. However, an interesting dichotomy

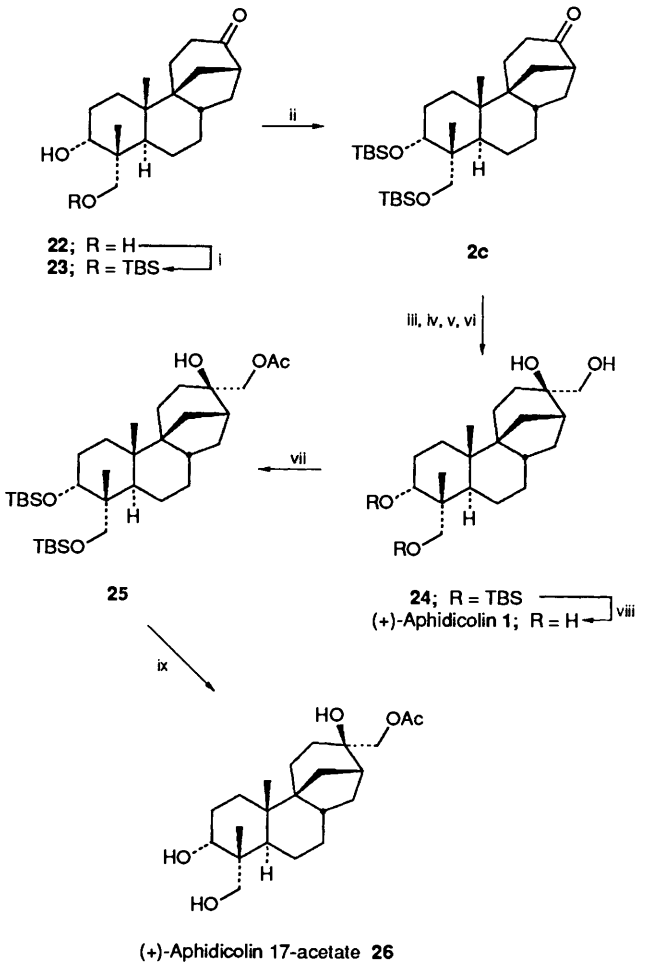


Reagents and conditions: i, $(F_3CSO_2)_2O$, CH_2Cl_2, 2,6-di-*tert*-butyl-4-methylpyridine; ii, Pd^0, CO, MeOH, DMF; iii, *m*-CPBA, or 2,5-dinitroperoxybenzoic acid, Na_2HPO_4, CH_2Cl_2, bis(2-*tert*-butyl-3-hydroxy-4-methylphenyl)sulphide; iv, LAH, THF, reflux; v, **21a**: BIO-RAD H^+ ion exchange resin, MeOH, reflux (100%), **21b**: AcOH, THF, H_2O, heat (70%).

arose during the evaluation of 3-deoxyaphidicolin and aphidicolin 17-acetate.[34] The 3-deoxy compound more strongly inhibited DNA polymerase α *in vitro*, whereas aphidicolin 17-acetate was more active *in vivo*. To reconcile these findings, a pro-drug mechanism involving partial *in vivo* hydrolysis of the acetate to aphidicolin was proposed. Indeed, aphidicolin 17-glycinate hydrochloride,[35] a more water-soluble derivative also believed to act as a pro-drug, is presently in clinical trials in Europe.[36]

These considerations led us to extend our approach to C-17 derivatives of aphidicolin; aphidicolin 17-acetate **26** served as the initial target. This effort would of course entail unmasking of the A-ring diol moiety under conditions that would leave the acetate intact. The acidic hydrolyses employed earlier for deprotection of **21a** and **21b** did not appear to be reasonable options. Thus, we turned our attention to the bis-*tert*-butyldimethylsilyl precursor **2c**.

Protection of 3α,18-dihydroxy-17-noraphidicolan-16-one **22** with *tert*-butyldimethylsilyl chloride and imidazole quantitatively furnished the monoprotected alcohol **23**. The requisite bissilyl ether **2c** could be prepared in 84% yield by exposure of either **22** or **23** to *tert*-butyldimethylsilyl triflate and triethylamine. The remaining transformations proceeded uneventfully. Quantitative conversion of **2c** into the corresponding enol triflate, followed by palladium(0)-catalysed carbonylation and epoxidation, afforded the epoxy ester as a

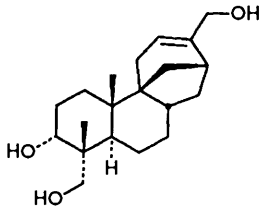


Reagents and conditions: i, TBSCl, imidazole, CH_2Cl_2 (100%); ii, TBSOTf, Et_3N, CH_2Cl_2 (84%); iii, triflation (100%); iv, carbonylation (80%); v, epoxidation (87%); vi, LAH, THF (96%); vii, Ac_2O, pyridine, DMAP, CH_2Cl_2 (98%); viii, HF, MeCN, CH_2Cl_2 (84%); ix, HF, MeCN, CH_2Cl_2 (86%)

ca. 15:1 mixture of diastereoisomers (highfield NMR analysis). Lithium aluminium hydride reduction followed by desilylation with HF in acetonitrile and methylene dichloride[37] then gave aphidicolin in 84% yield; the overall yield for the five-step conversion of **2c** into **1** was 61%. Alternatively, the diol **24** could be selectively monoacetylated to furnish **25** in 98% yield, whereupon treatment with HF in acetonitrile–methylene dichloride provided aphidicolin 17-acetate **26**. The synthesis of **26** from **2c** required six steps and proceeded in 57% overall yield.

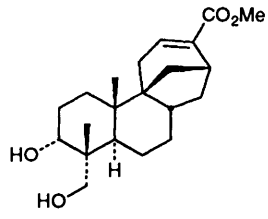
Synthesis and Biological Evaluation of 17-Methoxycarbonyl Congeners.—Another promising avenue for aphidicolin research involves the preparation of unnatural congeners, designed to retain the activity of **1** while offering enhanced water solubility and resistance to *in vivo* enzymatic deactivation. To this end, several groups have begun to explore structure–activity relationships in aphidicolin derivatives. The studies of McMurry *et al.* suggested that the rigidly held hydroxy groups at C-3 and C-16 are required for activity.[38] In contrast, Yoshioka and co-workers more recently reported significant *in vitro* inhibition of DNA polymerase α by allylic alcohol **27**, which lacks a 16-hydroxy group.[39]

The latter result prompted us to prepare the unsaturated ester **28** and the derived β-epoxy ester **29**, obtained in 92 and 84% yields *via* hydrolysis of the corresponding acetonides **19a** and **20a** (BIO-RAD H^+ ion exchange resin, methanol, reflux).

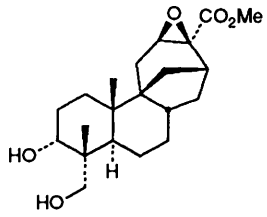


27

Neither **28** nor **29** inhibited growth of HeLa S_3 cells *in vitro*.* These findings are in accord with hypotheses linking the 16- and 17-hydroxy groups to the biological activity of aphidicolin and its derivatives.



28



29

Summary.—An efficient, stereocontrolled end game generated (+)-aphidicolin **1** from the 17-nor ketones **2a**, **2b** and **2c**. Both **2a** and **2b** served as intermediates in earlier total syntheses of **1**. The bis-*tert*-butyldimethylsilyl ether **2c** was also transformed to aphidicolin 17-acetate **26**, a naturally occurring derivative. The latter sequence should facilitate the preparation of other C(17) analogues which may evolve as clinically significant prodrugs.

Experimental

Methods and Materials.—All reactions were performed under an argon atmosphere, with distilled solvents in oven-dried glassware. THF was distilled from sodium–benzophenone ketyl, benzene was distilled from sodium, methylene dichloride, dimethyl sulphoxide, and acetonitrile were distilled from calcium hydride, and dimethylformamide was distilled from barium oxide. Reagent grade methanol was used without purification. Ether refers to diethyl ether. Reactions were monitored by thin-layer chromatography (TLC) using 0.25-mm E. Merck pre-coated silica gel plates. E. Merck silica gel, particle size 0.040–0.063 mm, was used for flash chromatography; distilled or HPLC grade solvents were employed as eluents.

M.p.s are corrected. Microanalyses were performed by Robertson Laboratories (Madison, NJ) or by the Rockefeller University Microanalytical Laboratory under the direction of S. T. Bella. *J* Values are quoted in Hz.

3α,18-*Dihydroxy*-17-*noraphidicolan*-16-*one* **22**.—To a solution of aphidicolin (250 mg, 0.740 mmol) in pyridine (11 ml) and water (5 ml) was added periodic acid (0.5 g, 2.20 mmol). The mixture was stirred at room temperature for 20 min and then poured over concentrated sulphuric acid (5 ml) and ice (50 ml). After extraction with ethyl acetate (× 3), the combined organic layers were washed with saturated aqueous sodium hydrogen carbonate and brine, dried ($MgSO_4$), filtered and concentrated. Residual pyridine was removed as an azeotrope with heptane on

* We thank Dr. Tomohisa Takita and co-workers, Nippon Kayaku Co., Ltd., Pharmaceuticals Group (Tokyo), for performing the *in vitro* evaluations of **28** and **29**.

a rotary evaporator. The thick oily residue typically was carried forward without purification. Crystallization from ether–light petroleum gave **22** (199 mg, 88%) as colourless needles, m.p. 157–158 °C (lit.,[1b] 155–156 °C); $[\alpha]_D^{20}$ −33.2° (*c* 0.25, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3610w, 3480br,w, 3000m, 2960s, 2870m, 1710s, 1460w, 1420w, 1060w and 1030w; δ_H(500 MHz, $CDCl_3$) 3.70 (s, 1 H), 3.48 (br s, 1 H), 3.40–3.32 (m, 2 H), 2.72 (br s, 1 H), 2.61 (dd, *J* 7.4 and 6.2, 1 H), 2.36 (ddd, *J* 17.1, 7.3 and 6.5, 1 H), 2.24 (d, *J* 8.6, 1 H), 2.23–2.18 (m, 1 H), 2.10–2.03 (m, 3 H), 2.00–1.89 (m, 3 H), 1.76–1.69 (m, 2 H), 1.58 (d, *J* 12.0, 1 H), 1.52–1.40 (m, 3 H), 1.34–1.26 (m, 1 H), 1.14–1.07 (m, 1 H), 1.03 (s, 3 H), 1.03–0.94 (m, 1 H) and 0.69 (s, 3 H); δ_C(125 MHz, $CDCl_3$) 215.9, 71.6, 49.0, 48.3, 41.2, 40.2, 39.6, 34.4, 34.0, 32.9, 31.6, 26.7, 25.9, 22.7, 21.7, 17.6 and 15.6; high resolution mass spectrum (Cl, ammonia) *m/z* 307.2240 $[(M + H)^+$; Calc. for $C_{19}H_{31}O_3$: 307.2280].

3α,18-*Isopropylidenedioxy*-17-*noraphidicolan*-16-*one* **2a**.—A sample of crude **22**, prepared *via* the above procedure, was dissolved in acetone (5 ml) and 2,2-dimethoxypropane (2 ml). A catalytic amount of toluene-*p*-sulphonic acid was added and the solution stirred at room temperature for 1 h. The reaction mixture then was neutralized with an excess of solid sodium hydrogen carbonate and filtered through a short pad of silica with ethyl acetate as eluent. Concentration followed by flash chromatography, with 20% ethyl acetate–hexanes as eluent, furnished **2a** (254 mg, 99%) as a white solid. An analytical sample was prepared by recrystallization from ether–light petroleum to give prisms, m.p. 143–145 °C (lit.,[1b] 143–146 °C); $[\alpha]_D^{20}$ −21.3° (*c* 0.80, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 2995s, 2945s, 2870s, 1710s, 1460m, 1390m, 1375m, 1260m, 1110s, 1095s, 1045m and 1085s; δ_H(500 MHz, $CDCl_3$) 3.67 (t, *J* 2.8, 1 H), 3.44 (ABq, J_{ab} = 12.2, $\Delta\nu_{ab}$ = 179.8, 2 H), 2.63 (t, *J* 5.7, 1 H), 2.39 (dd, *J* 9.8 and 2.8, 1 H), 2.37–2.30 (m, 1 H), 2.27 (dd, *J* 17.4 and 8.7, 1 H), 2.13–2.00 (m, 4 H), 1.93–1.85 (m, 2 H), 1.76 (m, 1 H), 1.68 (ddd, *J* 12.0, 5.7 and 1.2, 1 H), 1.60 (d, *J* 12.01, 1 H), 1.53 (m, 1 H), 1.51 (m, 1 H), 1.46 (dd, *J* 12.6 and 4.4, 1 H), 1.42 (s, 3 H), 1.34–1.25 (m, 1 H), 1.31 (ddd, *J* 12.8, 12.0 and 4.6, 1 H), 1.11 (m, 1 H), 1.07 (s, 3 H), 1.00 (td, *J* 12.9 and 2.3, 1 H) and 0.73 (s, 3 H); δ_C(125 MHz, $CDCl_3$) 215.5, 98.0, 73.4, 68.5, 49.0, 48.1, 41.4, 39.5, 34.6, 33.2, 32.9, 31.4, 29.8, 26.9, 25.9, 23.8, 21.7, 21.1, 18.9, 17.1 and 16.0; high resolution mass spectrum (CI, ammonia) *m/z* 364.2841 $[(M + NH_4)^+$; Calc. for $C_{22}H_{38}NO_3$: 364.2852].

3α,18-*Pivalyldioxy*-17-*noraphidicolan*-16-*one* **2b**.—A solution of the crude diol **22** (prepared as described above) in methylene dichloride (3.5 ml) was stirred at 0 °C, and pivalaldehyde (80 mg, 0.925 mmol) and a small crystal of toluene-*p*-sulphonic acid were added. After the mixture had been stirred at 0 °C for 1 h, it was quenched with saturated aqueous sodium hydrogen carbonate. The aqueous layer was extracted with ethyl acetate (×2) and the combined organic solutions were washed with brine, dried ($MgSO_4$), filtered and concentrated. Flash chromatography with 15% ethyl acetate–hexanes as eluent afforded **2b** (216 mg, 78%) as a colourless oil; $[\alpha]_D^{20}$ −28.0° (*c* 0.5, $CHCl_3$); $\nu(CHCl_3)/cm^{-1}$ 2960s, 2870m, 1710s, 1485w, 1460m, 1405w, 1390w, 1360w, 1325w, 1315w, 1115s, 1105s, 1065m, 1040m, 990m, 995w and 900w; δ_H(500 MHz, $CDCl_3$) 4.10 (s, 1 H), 3.92 (d, *J* 11.7, 1 H), 3.38 (br s, 1 H), 2.94 (d, *J* 11.7, 1 H), 3.37 (t, *J* 6.0, 1 H), 2.36–2.22 (m, 3 H), 2.14–2.00 (m, 4 H), 1.94–1.81 (m, 2 H), 1.77–1.75 (m, 1 H), 1.70 (dd, *J* 12.0 and 5.9, 1 H), 1.65–1.56 (m, 2 H), 1.59 (d, *J* 12.0, 1 H), 1.44 (ddd, *J* 25.0, 12.5 and 4.4, 1 H), 1.30 (ddd, *J* 25.1, 12.8 and 4.3, 1 H), 1.13–1.01 (m, 1 H), 1.08 (s, 3 H), 1.00–0.97 (m, 1 H), 0.93 (s, 9 H) and 0.68 (s, 3 H); δ_C(125 MHz, $CDCl_3$) 215.7, 107.5, 80.4, 75.3, 49.0, 48.2, 41.4, 39.7, 34.9, 34.5, 34.4, 33.5, 33.4, 31.5, 27.3, 26.0, 24.8, 24.1, 21.8, 21.2, 16.8 and 16.0; high resolution mass spectrum (CI, ammonia) *m/z* 375.2890 $[(M + H)^+$; Calc. for $C_{24}H_{39}O_3$: 375.2899].

18-tert-*Butyldimethylsilyloxy*-3α-*hydroxy*-17-*noraphidicolan*-16-*one* **23**.—To a stirred solution of the diol **22** (0.74 mmol) in DMF (3.0 ml) were added imidazole (126 mg, 1.85 mmol) and *tert*-butyldimethylsilyl chloride (223 mg, 1.48 mmol). After being stirred at room temperature for 36 h, the reaction mixture was quenched with water and diluted with ethyl acetate. The aqueous layer was extracted with ethyl acetate (×2), and the combined organic solutions were washed with water and brine, dried ($MgSO_4$), filtered and concentrated. Flash chromatography with 25% ethyl acetate–hexanes as eluent provided **23** (310 mg, 100%) as a colourless oil; $[\alpha]_D^{20}$ +1.0° (*c* 1.4, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3450m, 3000s, 2960s, 2870s, 1710s, 1470s, 1450s, 1420m, 1390m, 1370m, 1320m, 1260s, 1190w, 1160w, 1070s, 1000m, 970m, 940w, 930w, 910m and 830s; δ_H(500 MHz, $CDCl_3$) 4.32 (s, 1 H), 3.67 (m, 1 H), 3.46 (d, J_{ab} = 10.2, $\Delta\nu_{ab}$ = 107.6, 2 H), 2.63 (dd, *J* 5.7 and 3.1, 1 H), 2.30–2.14 (m, 4 H), 2.12–2.02 (m, 3 H), 1.81–1.73 (m, 3 H), 1.69–1.60 (m, 4 H), 1.40–1.33 (m, 3 H), 1.12–0.95 (m, 1 H), 1.06 (s, 3 H), 0.91 (s, 9 H), 0.71 (s, 3 H), 0.10 (s, 3 H) and 0.08 (s, 3 H); δ_C(125 MHz, $CDCl_3$) 215.6, 76.5, 71.4, 49.1, 48.0, 41.2, 40.1, 39.6, 34.7, 33.1, 32.6, 31.5, 26.7, 25.8, 25.6, 25.4, 21.7, 21.4, 17.8, 17.3, 15.9, −5.8 and −59.9; high resolution mass spectrum (CI, ammonia) *m/z* 421.3090 $[(M + H)^+$; Calc. for $C_{25}H_{45}O_3Si$: 421.3138].

3α,18-*Bis*-tert-*butyldimethylsilyloxy*-17-*noraphidicolan*-16-*one* **2c**.—A. *From* **23**. To a stirred solution of **23** (210 mg, 0.50 mmol) in methylene dichloride (2.5 ml) at −5 °C were added 2,4-dimethylpyridine (134 mg, 1.25 mmol) and *tert*-butyldimethylsilyl triflate (226 mg, 1.0 mmol). After 5 min, the reaction mixture was quenched with saturated aqueous sodium hydrogen carbonate and diluted with ethyl acetate. The organic phase was washed with 10% aqueous HCl and brine, dried ($MgSO_4$), filtered and concentrated. Flash chromatography with 10% ethyl acetate–hexanes as eluent gave **2c** (227 mg, 85%).

B. *From* **22**. A solution of crude diol **22** (*ca.* 0.74 mmol) in methylene dichloride (7.5 ml) was stirred at −5 °C and 2,6-dimethylpyridine (238 mg, 2.22 mmol) was added. Following dropwise introduction of *tert*-butyldimethylsilyl triflate (430 mg, 1.63 mmol), the reaction mixture was stirred for 5 min, quenched with saturated aqueous sodium hydrogen carbonate, and diluted with ethyl acetate. The organic layer was washed with 10% aqueous HCl and brine, dried ($MgSO_4$), filtered and concentrated. Flash chromatography with 10% ethyl acetate–hexanes as eluent afforded **2c** (332 mg, 84%) as a white solid. Crystallization by slow evaporation from ether gave needles, m.p. 125–128 °C; $[\alpha]_D^{20}$ +10.6° (*c* 0.5, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 2975s, 2930s, 2850m, 1710s, 1470m, 1460m, 1390w, 1360w, 1250m, 1070s, 1025w, 1000w, 975w, 940w, 830s and 715w; δ_H(500 MHz, $CDCl_3$) 3.67 (d, *J* 3.4, 1 H), 3.36 (ABq, J_{ab} = 9.1, $\Delta\nu_{ab}$ = 47.9, 2 H), 2.61 (t, *J* 6.44, 1 H), 2.31 (ddd, *J* 17.2, 5.8 and 4.6, 1 H), 2.22 (td, *J* 17.4 and 8.6, 1 H), 2.10–1.97 (m, 4 H), 1.85–1.76 (m, 3 H), 1.73–1.66 (m, 2 H), 1.58 (d, *J* 12.0, 1 H), 1.50–1.47 (m, 2 H), 1.40–1.27 (m, 2 H), 1.10–1.03 (m, 2 H), 1.04 (s, 3 H), 0.90 (s, 9 H), 0.89 (s, 9 H), 0.86 (s, 3 H), 0.06 (s, 3 H), 0.02 (s, 3 H) and 0.01 (s, 3 H); δ_C(125 MHz, $CDCl_3$) 215.7, 72.0, 69.9, 49.1, 48.1, 42.0, 40.9, 39.9, 36.8, 34.5, 33.4, 31.6, 26.9, 26.1, 26.0, 25.9, 25.3, 22.1, 21.9, 18.4, 18.2, 16.3, 16.1, −4.3, −5.0, −5.1 and −5.5; high resolution mass spectrum (CI, ammonia) *m/z* 535.3910 $[(M + H)^+$; Calc. for $C_{31}H_{59}O_3Si_2$: 535.4002] (Found: C, 69.65; H, 11.1. Calc. for $C_{31}H_{58}O_3Si_2$: C, 69.60; H, 10.94%).

16,17-*Epoxy*-3α,18-*isopropylidenedioxyaphidicolane* **3**.—A

suspension of sodium hydride (80%; 27 mg, 0.9 mmol) and trimethylsulphoxonium iodide (178 mg, 0.81 mmol) in DMSO (2.5 ml) was stirred at room temperature for 1 h, during which time it became homogeneous. A solution of **2a** (140 mg, 0.405 mmol) in THF (1 ml) was added dropwise and the reaction mixture then was heated to 70 °C for 3 h. After quenching with water and dilution with ethyl acetate, the layers were separated and the aqueous phase extracted with ethyl acetate (× 3). The combined organic solutions were washed with brine, dried ($MgSO_4$), filtered and concentrated. Flash chromatography with 20% ethyl acetate–hexanes as eluent afforded a mixture of the epoxides **3** (138 mg, 95%) as a thick oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 3000s, 2940s, 2870m, 1455m, 1390m, 1375m, 1205s, 1085s and 905m; δ_H(500 MHz, $CDCl_3$) 3.65 (d, *J* 12.0, 1 H), 3.63 (t, *J* 2.7, 1 H), 3.24 (d, *J* 12.0, 1 H), 2.70–2.55 (m, 3 H), 3.15–2.02 (m, 4 H), 1.94–1.85 (m, 3 H), 1.76–1.64 (m, 2 H), 1.61–1.56 (m, 3 H), 1.51–1.44 (m, 2 H), 1.41 (s, 6 H), 1.35–1.17 (m, 3 H), 1.01 (s, 3 H), 0.97–0.89 (m, 1 H) and 0.73 (s, 3 H); δ_C(125 MHz, $CDCl_3$) (assignments of diastereoisomeric pairs based on chemical shifts and relative intensities) 98.0; 73.5, 73.4; 68.8; 63.7, 63.1; 55.6, 54.1; 49.0, 48.7; 42.1, 41.8; 40.7, 40.5; 39.7, 39.6; 37.1; 35.3, 35.2; 33.6, 33.4; 31.9; 30.8; 29.6; 27.0, 26.9; 28.8, 26.7; 26.1, 25.7; 24.3, 24.2; 22.4; 19.1; 17.4, 17.3; 15.7, 15.5; high resolution mass spectrum (CI, isobutane) *m/z* 361.2708 [(M + H)$^+$; Calc. for $C_{23}H_{37}O_3$: 361.3743].

3α,18-*Isopropylidenedioxyaphidicol*-16-*ene* **6a**.—Butyllithium (2.90 mmol, 2.5 mol dm^{-3} in hexanes) was added dropwise to a stirred suspension of methyltriphenylphosphonium iodide (1.07 g, 3.0 mmol) in THF (15 ml). The mixture was stirred at room temperature for 2 h, and a solution of **2a** (200 mg, 0.578 mmol) in THF (2 ml) was introduced dropwise. After 12 h the reaction was quenched by the dropwise addition of water, the layers were separated and the aqueous phase extracted with ethyl acetate (× 2). The combined organic solutions were washed with brine, dried ($MgSO_4$), filtered and concentrated. Flash chromatography with 10% ether–hexanes as eluent gave **6a** (186 mg, 94%) which was recrystallized from methanol to give colourless needles: m.p. 133.5–136 °C (lit.,[1a] 134–135 °C); $[\alpha]_D^{20}$ −30.13° (*c* 0.75, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 2990m, 2940s, 2860m, 1650w, 1460m, 1390m, 1375m, 1255m, 1210m, 1150w, 1090m, 1050w, 990w, 880m and 850m; δ_H(500 MHz, $CDCl_3$) 4.48 (t, *J* 1.9, 1 H), 4.40 (s, 1 H), 3.65–3.62 (m, 2 H), 3.23 (d, *J* 12.1, 1 H), 2.70 (t, *J* 6.7, 1 H), 2.56 (dd, *J* 12.9 and 3.1, 1 H), 2.34–2.28 (m, 1 H), 2.14–1.98 (m, 4 H), 1.95–1.84 (m, 2 H), 1.75–1.63 (m, 3 H), 1.56–1.43 (m, 3 H), 1.43 (s, 3 H), 1.41 (s, 3 H), 1.28–1.20 (m, 2 H), 1.08 (dd, *J* 12.9 and 8.5, 1 H), 0.99 (s, 3 H), 0.88 (dt, *J* 12.8 and 3.3, 1 H) and 0.73 (s, 3 H); δ_C(125 MHz, $CDCl_3$) 155.7, 102.1, 98.0, 73.5, 68.8, 59.3, 43.3, 41.2, 39.7, 38.9, 35.2, 34.4, 33.4, 29.6, 28.2, 26.8, 26.4, 24.3, 22.3, 19.1, 17.4 and 15.6; high resolution mass spectrum (CI, ammonia) *m/z* 345.2810 [(M + H)$^+$; Calc. for $C_{23}H_{37}O_2$: 345.2793].

3α,18-*Isopropylidenedioxyaphidicolan*-17-*al* **17**.—A solution of 2,2,6,6-tetramethylpiperidine (40 mg, 0.28 mmol) in benzene (2.5 ml) was cooled to 0 °C and butyllithium (2.5 mol dm^{-3} in hexanes; 0.28 mmol) was added. After 5 min, diethylaluminium chloride (25 wt% in toluene; 0.28 mmol) was added, and the resulting slurry stirred at 0 °C for 0.5 h. A solution of the epoxides **3** (25 mg, 0.069 mmol) in benzene (1 ml) was then introduced dropwise. After the mixture had been stirred at 0 °C for 2 h and at room temperature for 1 h, the reaction was quenched with 10% aqueous HCl. The layers were separated and the aqueous phase extracted with ethyl acetate (× 3). The combined organic solutions were washed with saturated aqueous sodium hydrogen carbonate and brine, dried ($MgSO_4$), filtered and concentrated. Flash chromatography with 15% ethyl acetate–hexanes as eluent furnished an inseparable mixture of the aldehydes **17** (19 mg, 75%); $\nu_{max}(CHCl_3)/cm^{-1}$ 2990s, 2935s, 2850s, 1715s, 1450m, 1385m, 1370m, 1290s and 1080m; δ_H(500 MHz, $CDCl_3$) 9.69 and 9.59 (diastereoisomers, s, s, 1 H), 3.65 (d, *J* 12.0, 1 H), 3.62 (t, *J* 5.0, 2 H), 3.23 (d, *J* 12.0, 1 H), 2.64 (m, 1 H), 2.58 and 2.53 (diastereoisomers, d, d, *J* 2.9 and 2.8, 1 H), 2.32 and 2.21 (diastereoisomers, t, t, *J* 2.4 and 2.4, 1 H), 2.10–1.82 (m, 4 H), 1.80–1.53 (m, 6 H), 1.50–1.42 (m, 3 H), 1.41 (s, 3 H), 1.25–1.16 (m, 1 H), 1.16–1.06 (m, 1 H), 0.98 and 0.95 (diastereoisomers, s, s, 3 H), 0.89–0.80 (m, 1 H) and 0.73 and 0.71 (diastereoisomers, s, s, 3 H); δ_C(125 MHz, $CDCl_3$) (assignments of diastereoisomeric pairs based on chemical shifts and relative intensities) 204.8, 203.8; 98.0, 97.9; 73.4; 68.8, 68.7; 54.6, 54.3; 49.4, 49.2; 41.2, 40.6; 39.7, 39.6; 39.1; 35.3, 35.0; 34.2, 34.1; 33.8, 33.6; 33.4, 33.0; 29.7, 29.6; 29.5, 29.3; 27.5, 26.8; 26.6, 26.3; 25.6; 24.3, 24.1; 22.5, 22.2; 19.2, 19.0; 15.4; high resolution mass spectrum (CI, ammonia) *m/z* 361.2733 [(M + H)$^+$; Calc. for $C_{23}H_{37}O_3$: 361.2743].

17-*Hydroxy*-3α,18-*isopropylidenedioxyaphidicol*-15-*ene* **16**.—A solution of the epoxides **3** (20 mg, 0.056 mmol) and 2,6-dimethylpyridine (12 mg, 0.105 mmol) in methylene dichloride (1.0 ml) was cooled to −78 °C for 10 min, and then trimethylsilyl triflate (18.5 mg) was added. After the mixture had been stirred at −78 °C for 10 min the reaction was quenched with saturated aqueous sodium hydrogen carbonate. The layers were separated and the aqueous phase extracted with ethyl acetate (× 3). The combined organic solutions were washed with 10% aqueous HCl and brine, dried ($MgSO_4$), filtered and concentrated. Flash chromatography with 20% ethyl acetate–hexanes as eluent gave the allylic alcohol **16** (8 mg, 40%) and the aldehydes **17** (9 mg, 45%) as colourless oils. For **16**: $[\alpha]_D^{20}$ −10.9° (*c* 0.45, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3600w, 3450w, 3000s, 2935s, 2880s, 1450m, 1390m, 1375m, 1255m, 1200m, 1165m, 1085m, 1000m and 975m; δ_H(500 MHz, $CDCl_3$) 5.33 (s, 1 H), 4.02 (s, 2 H), 3.64 (d, *J* 11.9, 1 H), 3.23 (d, *J* 11.9, 1 H), 2.56–2.40 (m, 3 H), 2.32 (t, *J* 6.8, 1 H), 2.17–2.10 (m, 2 H), 2.01–1.97 (m, 1 H), 1.92–1.85 (m, 2 H), 1.68–1.48 (m, 4 H), 1.44 (s, 3 H), 1.42 (s, 3 H), 1.37–1.28 (m, 2 H), 1.26 (d, *J* 9.9, 1 H), 1.06 (s, 3 H), 1.03 (d, *J* 12.0, 1 H), 0.91 (dt, *J* 13.2 and 2.9, 1 H) and 0.71 (s, 3 H); δ_C(125 MHz, $CDCl_3$) 150.6, 120.6, 98.0, 73.6, 68.5, 65.5, 49.1, 42.2, 39.5, 39.1, 35.6, 35.0, 34.7, 31.9, 29.8, 27.6, 26.6, 25.6, 24.2, 21.7, 19.0, 17.2 and 16.5; high resolution mass spectrum (CI, ammonia) *m/z* 361.2724 [(M + H)$^+$; Calc. for $C_{23}H_{37}O_3$: 361.2743].

3α,18-*Isopropylidenedioxy*-16-(*trifluoromethylsulphonyloxy*)-17-*noraphidicol*-15-*ene* **18a**.—A solution of **2a** (116 mg, 0.335 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (0.570 mmol) in methylene dichloride (5 ml) was stirred at ambient temperature and triflic anhydride (142 mg, 0.503 mmol) was added dropwise. As the mixture was stirred for a further 1 h, a white precipitate formed. Following concentration at aspirator pressure on a rotary evaporator, the residue was taken up in ether. The white solid was then filtered off and washed with ether. Concentration of the filtrate and flash chromatography, with 10% ethyl acetate–hexanes as eluent, afforded **18a** (160 mg, 99%) as a colourless oil; $[\alpha]_D^{20}$ −12.4° (*c* 1.3, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 2990m, 2950m, 2870m, 1690w, 1415s, 1390m, 1370m, 1240s, 1200s, 1140s, 1080m, 1060s, 865m and 845m; δ(500 MHz, $CDCl_3$) 5.42 (m, 1 H), 3.65 (dd, *J* 2.8 and 2.5, 1 H), 3.60 (d, *J* 12.2, 1 H), 3.24 (d, *J* 22.2, 1 H), 2.60 (dd, *J* 18.8 and 4.7, 1 H), 2.53–2.41 (m, 3 H), 2.89 (m, 1 H), 1.75–1.68 (m, 2 H), 1.60–1.50 (m, 4 H), 1.42 (s, 6 H), 1.42–1.26 (m, 2 H), 1.08 (s, 3 H), 0.94 (ddd, *J* 12.7, 3.5 and 2.9, 1 H) and 0.71 (s, 3 H); δ_C(125 MHz, $CDCl_3$) 158.4 and 118.6 (q, *J* 320), 114.4, 100.0, 73.4, 68.4, 49.2, 41.8, 39.4, 38.5, 38.0, 36.5, 34.5, 34.6, 31.9, 29.9, 26.6, 25.3, 25.0, 24.0, 21.4, 18.9, 17.0 and 16.7; high resolution mass spectrum (CI, isobutane) *m/z* 479.2052 [(M + H)$^+$; Calc. for $C_{23}H_{34}O_5F_3S$: 479.2069]

(Found: C, 58.05; H, 7.1. Calc. for $C_{23}H_{33}O_5F_3S$: C, 57.72; H, 6.96%).

3α,18-(2,2-*Dimethylpropylidenedioxy*)-16-(*trifluoromethylsulphonyloxy*)-17-*noraphidicol*-15-*ene* **18b**.—The ketone **2b** (91 mg, 0.245 mmol) was subjected to triflation and work-up as described for the preparation of **18a**. Flash chromatography, with 10% ether–hexanes as eluent, gave **18b** (124 mg, 100%) as a colourless oil; $[\alpha]_D^{20}$ −14.1° (*c* 1.0, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 2960s, 2860m, 1730w, 1690w, 1590w, 1520m, 1420s, 1360m, 1250s, 1200m, 1140s, 1130s, 1110s, 1060s, 1050s, 990m, 910m and 870m; δ_H(500 MHz, $CDCl_3$) 5.38 (m, 1 H), 4.09 (s, 1 H), 3.90 (d, *J* 11.7, 1 H), 3.36 (s, 1 H), 2.93 (d, *J* 11.7, 1 H), 2.57 (dd, *J* 18.8 and 4.4, 1 H), 2.47 (t, *J* 5.5, 1 H), 2.43–2.36 (m, 3 H), 2.20–2.06 (m, 3 H), 1.87 (t, *J* 13.7, 1 H), 1.73–1.68 (m, 2 H), 1.64–1.48 (m, 4 H), 1.39–1.25 (m, 2 H), 1.08 (s, 3 H), 1.02–0.89 (m, 1 H), 0.94 (s, 9 H) and 0.67 (s, 3 H); δ_C(125 MHz, $CDCl_3$) 158.2, 118.6 (q, *J* 321), 114.6, 107.4, 80.4, 75.2, 49.2, 41.9, 39.6, 38.5, 38.0, 36.5, 34.9, 34.6, 32.6, 27.0, 25.6, 25.1, 24.8, 24.2, 21.4, 16.7 and 16.6; high resolution mass spectrum (CI, ammonia) *m/z* 507.2380 $[(M + H)^+$; Calc. for $C_{25}H_{38}O_5F_3S$: 507.2392].

3α,18-*Bis*-tert-*butyldimethylsilyloxy*-16-(*trifluoromethylsulphonyloxy*)-17-*noraphidicol*-15-*ene* **18c**.—The ketone **2c** (300 mg, 0.560 mmol) was subjected to triflation and work-up as described for the preparation of **18a**. Flash chromatography with 5% ether–hexanes as eluent furnished **18c** (370 mg, 99%) as a colourless oil; $[\alpha]_D^{20}$ −10.6° (*c* 0.8, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 2950s, 2930s, 2890m, 2860s, 1690w, 1470m, 1460m, 1420s, 1390m, 1360m, 1245s, 1140s, 1085s, 1060s, 1040s, 1015m, 1000m, 975w, 960w, 940w, 925w, 910m, 850s and 600m; δ_H(500 MHz, $CDCl_3$) 5.36 (m, 1 H), 3.65 (m, 1 H), 3.36 (ABq, J_{ab} = 9.1, $\Delta\nu_{ab}$ = 50.6, 2 H), 2.54–2.36 (m, 3 H), 2.10–2.02 (m, 3 H), 1.82 (d, *J* 13.8, 2 H), 1.67 (dd, *J* 10.5 and 5.2, 2 H), 1.53–1.41 (m, 4 H), 1.37–1.30 (m, 3 H), 1.03 (s, 3 H), 0.91 (s, 9 H), 0.88 (s, 9 H), 0.83 (s, 3 H), 0.05 (s, 6 H), 0.01 (s, 3 H) and −0.01 (s, 3 H); δ_C(125 MHz, $CDCl_3$) 158.3, 118.6 (q, *J* 320), 114.3, 71.9, 69.8, 49.2, 42.2, 41.3, 39.8, 38.6, 37.9, 36.6, 35.9, 26.6, 26.1, 26.0, 25.6, 25.5, 25.1, 22.2, 18.4, 18.2, 16.8, 16.3, −4.1, −5.1 and −5.5; high resolution mass spectrum (CI, ammonia) *m/z* 667.3450 $[(M + H)^+$; Calc. for $C_{32}H_{58}O_5F_3SSi_2$: 667.3495].

Methyl 3α,18-*Isopropylidenedioxyaphidicol*-15-*ene*-16-*carboxylate* **19a**.—The triflate **18a** (142 mg, 0.298 mmol), methanol (385 mg, 12 mmol) and triethylamine (61 mg, 0.60 mmol) were dissolved in DMF (2 ml). Carbon monoxide was bubbled through the solution for 10 min, and palladium(II) acetate (2 mg, 0.009 mmol) and triphenylphosphine (4.7 mg, 0.018 mmol) were then added. An atmosphere of carbon monoxide was maintained with stirring for 4 h as the colourless solution turned yellow and then red. The reaction mixture was quenched with water and extracted with ethyl acetate (×3). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated. Flash chromatography with 10% ethyl acetate–hexanes as eluent provided **19a** (87 mg, 75%) as a colourless oil; $[\alpha]_D^{20}$ −12.6° (*c* 1.6, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3100s, 2950s, 2870s, 1690s, 1650s, 1455s, 1435s, 1390s, 1360s, 1250s, 1220s, 1160m, 1070s, 1050m and 995m; δ_H(500 MHz, $CDCl_3$) 6.71 (m, 1 H), 3.71 (s, 3 H), 3.65 (t, *J* 2.9 Hz, 1 H), 3.64 (d, *J* 12.1, 1 H), 3.24 (d, *J* 12.1, 1 H), 2.98 (dd, *J* 6.0 and 7.3, 1 H), 2.71 (ddd, *J* 20.7, 4.8 and 1.5, 1 H), 2.56 (dd, *J* 20.8 and 3.1, 1 H), 2.43 (dd, *J* 12.8 and 2.8, 1 H), 2.16–2.00 (m, 3 H), 1.89 (tdd, *J* 11.8, 41.2 and 2.4, 1 H), 1.70 (m, 1 H), 1.63 (dd, *J* 5.7 and 10.7, 1 H), 1.53–1.46 (m, 4 H), 1.46 (s, 3 H), 1.44 (s, 3 H), 1.29 (m, 1 H), 1.19 (d, *J* 10.7, 1 H), 1.07 (s, 3 H), 1.00–0.72 (m, 3 H) and 0.67 (s, 3 H); δ_C(125 MHz, $CDCl_3$) 166.5, 142.9, 139.5, 97.9, 73.5, 68.4, 51.3, 49.0, 42.3, 39.2, 39.0, 35.5, 34.6, 32.8, 31.9, 29.8, 29.0, 26.4, 25.3, 24.0, 21.5, 18.9, 17.0 and 16.5; high resolution mass spectrum (CI, ammonia) *m/z* 406.2960 $[(M + NH_4)^+$; Calc. for $C_{24}H_{40}NO_4$: 406.2957] (Found: C, 73.8; H, 8.9. Calc. for $C_{24}H_{36}O_4$: C, 74.17; H, 9.27%).

Methyl 3α,18-(2,2-*Dimethylpropylidenedioxy*)*aphidicol*-15-*ene*-16-*carboxylate* **19b**.—The triflate **18b** (180 mg, 0.356 mmol) was dissolved in DMF (4 ml) and methanol (0.06 ml). Carbon monoxide was bubbled through the solution for 10 min, and triethylamine (101 mg), palladium(II) acetate (3 mg, 0.01 mmol) and triphenylphosphine (7 mg, 0.03 mmol) were then added. Carbon monoxide was bubbled through the solution for an additional 10 min. Further reaction and work-up as described for **19a**, followed by flash chromatography with 10% ethyl acetate–hexanes as eluent, afforded **19b** (114 mg, 77%) as a colourless oil; $[\alpha]_D^{20}$ −11.5° (*c* 0.85, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 2950s, 2860m, 1700s, 1645m, 1485w, 1460m, 1435m, 1405w, 1390w, 1360w, 1315w, 1260s, 1125m, 1110s, 1080m, 960m and 890m; δ_H(500 MHz, $CDCl_3$) 6.68 (t, *J* 3.1, 1 H), 4.10 (s, 1 H), 3.91 (d, *J* 11.7, 1 H), 3.71 (s, 3 H), 3.36 (t, *J* 2.7, 1 H), 2.97 (t, *J* 6.7, 1 H), 2.93 (d, *J* 11.7, 1 H), 2.69 (dd, *J* 20.9 and 3.4, 1 H), 2.48 (dd, *J* 20.9 and 3.1, 1 H), 2.38 (dd, *J* 13.0 and 3.1, 1 H), 2.16–2.02 (m, 3 H), 2.0 (ddt, *J* 14.0, 2.4 and 1.8, 1 H), 1.70–1.60 (m, 4 H), 1.47 (dq, *J* 12.8 and 4.6, 1 H), 1.36–1.24 (m, 2 H), 1.18 (d, *J* 10.7, 1 H), 1.08 (s, 3 H), 1.04–0.91 (m, 1 H), 0.95 (s, 9 H) and 0.67 (s, 3 H); δ_C(125 MHz, $CDCl_3$) 166.7, 142.8, 139.7, 107.3, 80.5, 75.3, 51.4, 49.0, 42.4, 39.5, 39.1, 35.6, 34.9, 34.5, 32.9, 32.6, 29.4, 26.9, 25.4, 24.8, 24.2, 21.6, 16.8 and 16.5; high resolution mass spectrum (CI, ammonia) *m/z* 417.3005 $[(M + H)^+$; Calc. for $C_{26}H_{41}O_4$: 417.3030] (Found: C, 75.1; H, 9.65. Calc. for $C_{26}H_{40}O_4$: C, 74.95; H, 9.61%).

Methyl 3α,18-*Bis*-tert-*butyldimethylsilyloxyaphidicol*-15-*ene*-16-*carboxylate* **19c**.—The triflate **18c** (350 mg, 0.526 mmol) and methanol (67 mg, 2.1 mmol) were dissolved in DMF (3.5 ml). Further reaction and work-up as described for **19b**, followed by flash chromatography with 5% ethyl acetate–hexanes as eluent, gave **19c** (245 mg, 80%) as a colourless oil; $[\alpha]_D^{20}$ −9.7° (*c* 0.65, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 2960s, 2930s, 2860s, 1705s, 1650m, 1470m, 1460m, 1385m, 1360m, 1310w, 1250s, 1080s, 1015m, 1000m, 975m, 950w, 940w and 830s; δ_H(500 MHz, $CDCl_3$) 6.66 (s, 1 H), 3.70 (s 3, H), 3.66 (d, *J* 2.7, 1 H), 3.38 (ABq, J_{ab} 9.1, $\Delta\nu_{ab}$ = 60.4, 2 H), 2.94 (t, *J* 5.3, 1 H), 2.53 (ABX, J_{ab} 20.9, J_{ax} 4.4, J_{bx} = 3.0, $\Delta\nu_{ab}$ = 98.2, 2 H), 2.10–2.00 (m, 3 H), 1.82–1.72 (m, 2 H), 1.68–1.61 (m, 2 H), 1.51–1.41 (m, 3 H), 1.40–1.32 (m, 3 H), 1.17 (d, *J* 10.7, 1 H), 1.03 (s, 3 H), 0.91 (s, 9 H), 0.88 (s, 9 H), 0.83 (s, 3 H), 0.05 (s, 3 H), 0.04 (s, 3 H), 0.01 (s, 3 H) and −0.01 (s, 3 H); δ_H(125 MHz, $CDCl_3$) 166.7, 143.0, 139.7, 71.9, 69.7, 51.4, 49.0, 42.1, 41.9, 39.6, 39.2, 35.7, 35.6, 32.8, 29.4, 26.5, 26.1, 26.0, 25.5, 25.4, 22.2, 18.4, 18.2, 16.7, 16.3, −4.2, −5.0 and −5.5; high resolution mass spectrum (CI, ammonia) *m/z* 577.4080 $[(M + H)^+$; Calc. for $C_{33}H_{61}O_4Si_2$: 577.4108] (Found: C, 68.5; H, 10.35. Calc. for $C_{33}H_{60}O_4Si_2$: C, 68.70; H, 10.49%).

Methyl 15β,16β-*Epoxy*-3α,18-*isopropylidenedioxyaphidicolane*-16α-*carboxylate* **20a**.—To a stirred mixture of the enolate **19a** (16 mg, 0.041 mmol), disodium phosphate (58.4 mg, 0.412 mmol), bis(2-*tert*-butyl-3-hydroxy-4-methylphenyl)-sulphide (5 mg) and methylene dichloride (2 ml) was added *m*-chloroperoxybenzoic acid (100%; 56.8 mg, 0.328 mmol). The reaction mixture was heated at reflux for 8 h, cooled to room temperature, and quenched with saturated aqueous sodium hydrogen carbonate. The aqueous layer was extracted with ethyl acetate (×3), and the combined organic solutions were washed with brine, dried ($MgSO_4$), filtered and concentrated. Flash chromatography with 10% ethyl acetate–hexanes as eluent furnished **20a** (15 mg, 90%) as a white powder.

Recrystallization from ether–hexane gave needles, m.p. 168–170 °C; $[\alpha]_D^{20}$ −1.9° (*c* 0.95, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 2990s, 2935s, 2870s, 1740s, 1435m, 1385m, 1370m, 1280m, 1255m, 1205s, 1195s, 1090s and 1075m; δ_H(500 MHz, $CDCl_3$) 3.73 (s, 3 H), 3.65 (t, *J* 2.92, 1 H), 3.58 (d, *J* 12.1, 1 H), 3.35 (d, *J* 3.9, 1 H), 3.23 (d, *J* 12.2, 1 H), 2.75 (t, *J* 6.5, 1 H), 2.41 (d, *J* 16.4, 1 H), 2.30 (dd, *J* 13.0 and 3.0, 1 H), 2.20–1.98 (m, 4 H), 1.85 (tdd, *J* 11.7, 4.1 and 2.4, 1 H), 1.72 (m, 1 H), 1.65 (d, *J* 11.5, 1 H), 1.54–1.43 (m, 2 H), 1.43 (s, 3 H), 1.41 (s, 3 H), 1.30–1.20 (m, 2 H), 1.10 (dd, *J* 13.4 and 9.9, 1 H), 0.96 (s, 3 H), 0.90 (dt, *J* 13.1 and 2.7, 1 H) and 0.68 (s, 3 H); δ_C(125 MHz, $CDCl_3$) 171.0, 97.9, 73.4, 68.4, 62.7, 57.3, 52.3, 47.8, 41.0, 39.3, 34.6, 33.9, 33.3, 32.1, 29.8, 29.1, 26.4, 26.2, 24.2, 24.0, 21.3, 18.9, 17.0 and 15.3; high resolution mass spectrum (CI, ammonia) *m/z* 422.2876 $[(M + NH_4)^+$; Calc. for $C_{24}H_{40}NO_5$: 422.2907] (Found: C, 71.05; H, 8.8. Calc. for $C_{24}H_{36}O_5$: C, 71.24; H, 8.98%).

Methyl 15β,16β-*Epoxy*-3α,18-(2,2-*Dimethylpropylidenedioxy*)*aphidicolane*-16α-*carboxylate* **20b**.—A mixture of the enolate **19b** (40 mg, 0.096 mmol), disodium phosphate (41 mg, 0.288 mmol), bis(2-*tert*-butyl-3-hydroxy-4-methylphenyl)-sulphide (5 mg), and methylene dichloride (1 ml) was treated with 2,5-dinitroperoxybenzoic acid (32 mg, 0.144 mmol). The reaction mixture was stirred at room temperature for 2 h, and then quenched with saturated aqueous sodium hydrogen carbonate and diluted with ethyl acetate. The aqueous layer was extracted with ethyl acetate (×3) and the combined organic solutions were washed with brine, dried ($MgSO_4$), filtered and concentrated. Flash chromatography with 10% ethyl acetate–hexanes as eluent gave **20b** (32 mg, 75%) as a colourless oil; $[\alpha]_D^{20}$ −0.8° (*c* 0.50, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 2960s, 2870m, 1735s, 1485m, 1460m, 1440m, 1405m, 1385m, 1360m, 1350m, 1320w, 1290m, 1270m, 1170w, 1125s, 1110s, 1085m, 1050m, 990m and 905w; δ_H(500 MHz, $CDCl_3$) 4.08 (s, 1 H), 3.88 (d, *J* 11.7, 1 H), 3.72 (s, 3 H), 3.34 (m, 2 H), 2.91 (d, *J* 11.7, 1 H), 2.75 (t, *J* 6.6, 1 H), 2.38 (d, *J* 16.5, 1 H), 2.26 (dd, *J* 13.0 and 3.1, 1 H), 2.15–2.08 (m, 3 H), 2.04–1.96 (m, 1 H), 1.88–1.81 (m, 1 H), 1.74–1.70 (m, 1 H), 1.65 (d, *J* 11.6, 1 H), 1.63–1.51 (m, 2 H), 1.41 (ddd, *J* 25.7, 12.8 and 4.7, 1 H), 1.30–1.23 (m, 2 H), 1.10 (dd, *J* 9.6 and 9.8, 1 H), 0.97 (s, 3 H), 0.94 (s, 9 H), 0.91–0.88 (m, 1 H) and 0.64 (s, 3 H); δ_C(125 MHz, $CDCl_3$) 171.0, 107.3, 80.4, 75.2, 62.3, 57.3, 52.5, 47.8, 41.1, 39.5, 34.9, 34.5, 33.9, 33.3, 32.8, 29.2, 26.9, 26.2, 24.7, 24.5, 24.1, 21.4, 16.7 and 15.4; high resolution mass spectrum (CI, ammonia) *m/z* 450.3220 $[(M + NH_4)^+$; Calc. for $C_{26}H_{44}NO_5$: 450.3219] (Found: C, 71.8; H, 9.2. Calc. for $C_{26}H_{40}O_5$: C, 72.17; H, 9.25%).

Methyl 15β,16β-*Epoxy*-3α,18-*bis*-tert-*butyldimethylsilyloxy*-*aphidicolane*-16α-*carboxylate* **20c**.—A stirred mixture of the enolate **19c** (92 mg, 0.160 mmol), disodium phosphate (68 mg, 0.479 mmol), bis(2-*tert*-butyl-3-hydroxy-4-methylphenyl)-sulphide (5 mg) and methylene dichloride (1 ml) was treated with *m*-chloroperoxybenzoic acid (100%; 55 mg, 0.320 mmol) and heated at reflux for 8 h. Work-up as described for **20a** followed by flash chromatography, with 10% ethyl acetate–hexanes as eluent, provided **20c** (84 mg, 87%) as a colourless oil; $[\alpha]_D^{20}$ −1.8° (*c* 1.00, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 2960s, 2940s, 2890s, 2860s, 1735s, 1470m, 1450m, 1440m, 1390m, 1360m, 1355m, 1320w, 1290m, 1255s, 1185w, 1140m, 1090s, 1040s, 1020m, 1000m, 980m, 950m, 935w, 890m and 835s; δ_H(500 MHz, $CDCl_3$) 3.71 (s, 3 H), 3.25 (d, *J* 2.6, 1 H), 3.33 (ABq, J_{ab} 9.1, $\Delta\nu_{ab}$ = 43.3, 2 H), 3.31 (d, *J* 3.7, 1 H), 2.71 (dd, *J* 6.7 and 6.5, 1 H), 2.32 (d, *J* 16.4, 1 H), 2.15–2.00 (m, 3 H), 1.96–1.85 (m, 1 H), 1.82–1.72 (m, 1 H), 1.71–1.64 (m, 2 H), 1.62 (d, *J* 11.6, 1 H), 1.50–1.41 (m, 1 H), 1.36–1.18 (m, 4 H), 1.52 (dd, *J* 10.3 and 9.7, 1 H), 0.91 (s, 3 H), 0.90 (s, 9 H), 0.86 (s, 9 H), 0.84–0.78 (m, 1 H), 0.79 (s, 3 H), 0.05 (s, 3 H), 0.03 (s, 3 H), −0.015 (s, 3 H) and −0.024 (s, 3 H); δ_C(125 MHz, $CDCl_3$) 171.1, 71.9, 69.9, 62.7, 57.4, 52.3, 47.8, 42.2, 40.6, 39.7, 36.2, 34.0, 33.1, 29.2, 26.5, 26.3, 26.1, 26.0, 25.5, 24.5, 22.1, 18.4, 18.2, 16.2, 15.5, −4.1, −5.0, −5.1 and −5.5; high resolution mass spectrum (CI, ammonia) *m/z* 593.4038 $[(M + H)^+$: Calc. for $C_{33}H_{61}O_5Si_2$: 593.4061] (Found: C, 67.05; H, 10.35. Calc. for $C_{33}H_{60}O_5Si_2$: C, 66.85; H, 10.21%).

3α,18-*Isopropylidenedioxyaphidicolin* **21a**.—A solution of the epoxy ester **20a** (16 mg, 0.040 mmol) in THF (1.5 ml) was stirred at room temperature. Upon addition *via* a syringe of lithium aluminium hydride (1 mol dm^{-3} in THF; 0.20 mmol), an exothermic reaction occurred immediately. The solution then was heated at reflux for 1 h, cooled to room temperature, and quenched with water (8 μl) followed by NaOH (3 mol dm^{-3}; 8 μl) and water (24 μl). After vigorous stirring of the mixture, the white precipitates were filtered off and washed with ethyl acetate. The filtrate was dried ($MgSO_4$), filtered and concentrated. The solid residue was purified by flash chromatography with 50% ethyl acetate–hexanes as eluent, to give **21a** (15 mg, 100%) as a white solid. Recrystallization by slow evaporation from ether gave colourless microcrystalline plates, m.p. 160–162 °C; $[\alpha]_D^{20}$ −10.0° (*c* 0.70 $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3570w, 3440w, 2990s, 2940s, 2870s, 1665w, 1455m, 1385m, 1370m, 1250m, 1200s, 1150m, 1085s, 1065m and 1040m; δ_H(500 MHz, $CDCl_3$) 3.64 (d, *J* 12.0, 1 H), 3.63 (t, *J* 2.7, 1 H), 3.46 (d, *J* 11.0, 1 H), 3.37 (d, *J* 12.0, 1 H), 3.23 (d, *J* 12.0, 1 H), 2.59 (dd, *J* 13.0 and 3.1, 1 H), 2.17 (t, *J* 6.7, 1 H), 2.10 (dt, *J* 13.1 and 3.4, 1 H), 2.00–1.95 (m, 2 H), 1.91–1.86 (m, 2 H), 1.85–1.75 (m, 1 H), 1.72 (d, *J* 11.3, 1 H), 1.70–1.60 (m, 1 H), 1.57–1.53 (m, 2 H), 1.51–1.44 (m, 3 H), 1.41 (s, 6 H), 1.39–1.30 (m, 2 H), 1.25 (s, 1 H), 1.20 (dd, *J* 12.7 and 4.0, 1 H), 1.00 (s, 3 H), 0.96–0.90 (m, 2 H) and 0.72 (s, 3 H); δ_C(125 MHz, $CDCl_3$) 98.0, 74.6, 73.5, 68.8, 68.0, 49.2, 41.1, 40.0, 39.6, 35.2, 33.4, 32.7, 31.3, 30.5, 28.5, 27.0, 26.7, 24.5, 24.3, 22.6, 19.1, 17.4 and 15.5; high resolution mass spectrum (CI, ammonia) *m/z* 379.2823 $[(M + H)^+$; Calc. for $C_{23}H_{39}O_4$: 379.2848] (Found: C, 72.75; H, 10.0. Calc. for $C_{23}H_{38}O_4$: C, 72.96: H, 10.12%).

15β,16β-*Epoxy*-3α,18-*Isopropylidenedioxyaphidicolan*-17-*ol* **15**.—A stirred solution of **20a** (18 mg, 0.045 mmol) in THF (1 ml) was cooled to 0 °C. After addition of 0.070 mmol of lithium aluminium hydride (1 mol dm^{-3} in THF; 0.070 mmol), the reaction mixture was stirred at 0 °C for 0.5 h and then subjected to work-up as described for **21b**. Preparative TLC with 50% ethyl acetate–hexanes as eluent afforded **15** (10 mg, 60%) as an oil and **21a** (6 mg, 35%) as a white powder. For **15**: $[\alpha]_D^{20}$ −13.0° (*c* 0.50, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3650–3300w, 2995s, 2965s, 2880s, 1455m, 1390m, 1375m, 1235m, 1195m, 1085m, 1055m and 995m; δ_H(500 MHz, $CDCl_3$) 3.78 (d, *J* 12.5, 1 H), 3.63 (m, 2 H), 3.58 (d, *J* 12.2, 1 H), 3.22 (d, *J* 12.2, 1 H), 3.13 (d, *J* 3.6, 1 H), 2.35 (d, *J* 16.6, 1 H), 2.33 (dd, *J* 13.1 and 3.1, 1 H), 2.24 (t, *J* 6.0, 1 H), 2.18–2.05 (m, 2 H), 2.05–1.95 (m, 2 H), 1.85 (t, *J* 13.8, 1 H), 1.70 (d, *J* 11.2, 1 H), 1.67–1.58 (m, 1 H), 1.51 (dd, *J* 13.9 and 2.7, 2 H), 1.42 (s, 3 H), 1.41 (s, 3 H), 1.30–1.18 (m, 4 H), 1.05–1.00 (m, 1 H), 0.96 (s, 3 H), 0.91–0.86 (m, 1 H) and 0.68 (s, 3 H); δ_C(125 MHz, $CDCl_3$) 97.9, 73.5, 68.4, 66.8, 61.5, 55.1, 48.1, 40.9, 39.4, 34.7, 33.7, 32.9, 32.2, 29.8, 29.2, 26.5, 26.3, 24.2, 24.0, 21.4, 18.9, 17.0 and 15.4; high resolution mass spectrum (CI, ammonia) *m/z* 379.2651 $[(M + H)^+$; Calc. for $C_{23}H_{35}O_4$: 379.2692].

3α,18-(2,2-*Dimethylpropylidenedioxy*)*aphidicolin* **21b**.—A solution of **20b** (29 mg, 0.067 mmol) in THF (0.70 ml) was treated with lithium aluminium hydride (1.0 mol dm^{-3} in THF; 0.33 mmol), causing an immediate exothermic reaction. The solution was heated at reflux for 1 h, cooled to room temperature, and quenched by the cautious dropwise addition of saturated aqueous sodium sulphate. After dilution with ethyl

acetate and separation of the layers, the aqueous phase was extracted with ethyl acetate (×3). The combined organic solutions were washed with saturated brine, dried ($MgSO_4$), filtered and concentrated. Flash chromatography with 50% ethyl acetate–hexanes as eluent furnished **21b** (27 mg, 100%) as a colourless oil; $[\alpha]_D^{20}$ −10.5° (*c* 1.1, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3670w, 3450w, 2970s, 1480m, 1460m, 1405m, 1390m, 1365m, 1315w, 1240w, 1125s, 1110s, 1075s, 1035s, 980m, 960m, 930w and 900w; δ_H(500 MHz, $CDCl_3$) 4.08 (s, 1 H), 3.94 (d, *J* 11.7, 1 H), 3.45 (d, *J* 11.0, 1 H), 3.37 (d, *J* 11.0, 1 H), 3.34 (d, *J* 3.4, 1 H), 2.90 (d, *J* 11.7, 1 H), 2.58 (dd, *J* 2.8 and 12.8, 1 H), 2.17 (t, *J* 6.6, 1 H), 2.10 (dt, *J* 3.3 and 13.2, 1 H), 2.05–1.95 (m, 3 H), 1.90–1.70 (m, 4 H), 1.72 (d, *J* 11.4, 1 H), 1.68 (dd, *J* 3.1 and 12.1, 1 H), 1.62–1.55 (m, 2 H), 1.46 (dd, *J* 14.0 and 5.7, 1 H), 1.43–1.24 (m, 4 H), 1.20 (dd, *J* 12.6 and 3.9, 1 H), 1.00 (s, 3 H), 0.98–0.89 (m, 1 H), 0.92 (s, 9 H) and 0.67 (s, 3 H); δ_C(125 MHz, $CDCl_3$) 107.2, 80.3, 75.4, 74.6, 67.9, 49.1, 41.1, 40.0, 39.8, 34.92, 34.90, 33.7, 32.6, 31.3, 28.4, 27.1, 27.0, 24.7, 24.6, 24.4, 22.5, 16.9 and 15.5; high resolution mass spectrum (CI, ammonia) *m/z* 406.2960 [M^+; Calc. for $C_{25}H_{42}O_4$: 406.3081].

3α,18-*Bis*-tert-*butyldimethylsilyloxyaphidicolin* **24**.—To a stirred solution of **20c** (69 mg, 0.12 mmol) in THF (3 ml) was added lithium aluminium hydride (1.0 mol dm^{-3} in THF; 0.30 mmol), causing an immediate exothermic reaction. Further reaction, work-up, and flash chromatography as described for **21b** gave **24** (66 mg, 96%) as a colourless oil; $[\alpha]_D^{20}$ −8.0° (*c* 1.00, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3580w, 3440w, 2950s, 2860s, 1475s, 1465m, 1390m, 1360m, 1250s, 1180w, 1090s, 1025m, 1005m, 975m, 945m, 890m and 830s; δ_H(500 MHz, $CDCl_3$) 6.62–6.60 (m, 1 H), 3.40 (ABq, J_{ab} 10.1, $\Delta\nu_{ab}$ 27.8, 2 H), 3.36 (ABq, J_{ab} 9.1, $\Delta\nu_{ab}$ 53.7, 2 H), 2.14 (t, *J* 6.5, 1 H), 2.11–2.03 (m, 1 H), 1.97–1.84 (m, 4 H), 1.82–1.72 (m, 3 H), 1.68 (d, *J* 11.3, 1 H), 1.67–1.60 (m, 1 H), 1.47–1.36 (m, 4 H), 1.33–1.27 (m, 1 H), 1.24–1.19 (m, 2 H), 0.94 (s, 9 H), 0.88 (s, 3 H), 0.87 (s, 9 H), 0.83 (s, 3 H), 0.04 (s, 3 H), 0.03 (s, 3 H), −0.03 (s, 3 H) and −0.10 (s, 3 H); δ_C(125 MHz, $CDCl_3$) 74.7, 72.0, 70.1, 68.0, 49.1, 42.5, 41.0, 40.0, 39.5, 37.1, 32.8, 31.4, 28.4, 27.1, 26.5, 26.1, 26.0, 25.8, 24.5, 23.2, 18.4, 18.2, 16.4, 15.5, −4.3, −5.0, −5.1 and −5.5; high resolution mass spectrum (CI, ammonia) *m/z* 567.4283 [$(M + H)^+$; Calc. for $C_{32}H_{63}O_4Si_2$: 567.4265].

Aphidicolin **1**.—A. *From* **21a**. A mixture of **21a** (15 mg, 0.042 mmol), BIO-RAD AG50W-X2 50–100 mesh H^+ ion exchange resin (20 mg), and methanol (2 ml) was heated at reflux for 2 h, cooled and filtered through a short pad of Celite, washing with ethyl acetate. After evaporation of solvent, the solid residue was recrystallized from ethyl acetate to give aphidicolin (14 mg, 100%) as colourless prisms.

B. *From* **21b**. A solution of **21b** (19 mg, 0.047 mmol) in a mixture of THF (0.4 ml), acetic acid (0.4 ml), and water (0.2 ml) was heated at 60 °C for 36 h, cooled, diluted with ethyl acetate and washed with water. The aqueous layer was extracted with ethyl acetate (×3) and the combined organic solutions were dried ($MgSO_4$), filtered and concentrated. The residue was dissolved in methanol, and heptane was added and evaporated to remove any residual acetic acid. Preparative TLC with 75% ethyl acetate–hexanes as eluent afforded aphidicolin (11 mg, 70%) as a white solid.

C. *From* **24**. A solution of **24** (14 mg, 0.025 mmol) in methylene dichloride (0.30 ml) and acetonitrile (0.30 ml) was cooled to −5 °C and 1 drop of 48% hydrofluoric acid was added. After 5 min the ice–salt bath was removed and stirring was continued for 20 min. The reaction mixture was quenched with saturated aqueous sodium hydrogen carbonate and diluted with ethyl acetate. The layers were separated and the aqueous phase extracted with ethyl acetate (×3). The combined organic solutions were dried ($MgSO_4$), filtered and concentrated. Crystallization from ethyl acetate then furnished 7 mg of aphidicolin (7 mg, 90%) as colourless prisms, m.p. 226–228 °C (lit.,[1] 227–223 °C); $[\alpha]_D^{20}$ 12° (*c* 0.25, methanol); ν_{max}(KBr)/cm^{-1} 3500s, 3350br,s, 2980s, 2950s, 2890s, 1475m, 1080m, 1050m, 1030m, 965m and 890w; δ_H(500 MHz, [$^2H_5$]-pyridine) 3.93 (s, 1 H), 3.83 (d, *J* 10.8, 1 H), 3.81 (dd, *J* 10.8 and 3.8, 1 H), 3.73 (dd, *J* 12.7 and 5.4, 1 H), 3.64 (dd, *J* 10.9 and 2.8, 1 H), 2.90 (dd, *J* 12.7 and 2.8, 1 H), 2.58 (dd, *J* 6.7 and 6.5, 1 H), 2.52 (dd, *J* 13.2 and 3.4, 1 H), 2.35 (d, *J* 10.9, 1 H), 2.30 (dd, *J* 12.0 and 7.4, 1 H), 2.24–2.20 (m, 1 H), 2.06–1.95 (m, 2 H), 1.84–1.61 (m, 6 H), 1.51–1.37 (m, 2 H), 1.29 (dq, *J* 12.6 and 4.1, 1 H), 1.15 (dd, *J* 13.3 and 8.0, 1 H), 1.05–1.00 (m, 1 H), 1.04 (s, 3 H) and 0.80 (s, 3 H); δ_C(125 MHz, [$^2H_5$]pyridine) 76.3, 74.2, 71.9, 68.3, 49.7, 42.2, 41.0, 40.5, 40.2, 34.1, 33.4, 31.8, 29.1, 27.5, 27.3, 27.2, 25.6, 2.5, 18.1 and 15.5; high resolution mass spectrum (CI, ammonia) *m/z* 338.2482 [M^+; Calc. for $C_{20}H_{34}O_4$: 338.2457] (Found: C, 70.7; H, 10.05. Calc. for $C_{20}H_{34}O_4$: C, 70.95, H, 10.13%).

3α,18-*Bis*-tert-*butyldimethylsilyloxyaphidicolin* 17-*Acetate* **25**.—A stirred solution of **24** (66 mg, 0.12 mmol) in methylene dichloride (1.2 ml) was treated with DMAP (3 mg), pyridine (37 mg, 0.47 mmol), and acetic anhydride (24 mg, 0.23 mmol). After 30 min, the reaction mixture was quenched with water and diluted with ethyl acetate. The aqueous layer was extracted with ethyl acetate (×2) and the combined organic solutions were washed with brine, dried ($MgSO_4$), filtered and concentrated. Flash chromatography with 20% ethyl acetate–hexanes as eluent afforded 70 mg of **25** (70 mg, 98%) as a white solid. Recrystallization by slow evaporation from ether gave colourless needles, m.p. 156–159 °C; $[\alpha]_D^{20}$ −4.6° (*c* 0.55, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3580w, 2950s, 2930s, 2825s, 1725s, 1470m, 1460m, 1385m, 1360m, 1250s, 1080s, 1065s, 1030m, 1015m, 1000m, 970w, 905w, 885w and 830s; δ_H(500 MHz, $CDCl_3$) 3.94 (ABq, J_{ab} 11.3, $\Delta\nu_{ab}$ 28.0, 2 H), 3.60 (d, *J* 1.9, 1 H), 3.35 (ABq, J_{ab} 9.1, $\Delta\nu_{ab}$ 50.4, 2 H), 2.07 (s, 3 H), 2.07–2.02 (m, 3 H), 1.93–1.71 (m, 6 H), 1.63–1.59 (m, 2 H), 1.52–1.38 (m, 3 H), 1.36–1.31 (m, 2 H), 1.26–1.16 (m, 3 H), 0.92 (s, 3 H), 0.87 (s, 9 H), 0.86 (s, 9 H), 0.82 (s, 3 H), 0.02 (s, 3 H), 0.018 (s, 3 H), −0.014 (s, 3 H) and −0.025 (s, 3 H); δ_C(125 MHz, $CDCl_3$) 171.2, 73.5, 72.0, 71.2, 70.0, 49.0, 42.5, 41.6, 40.0, 39.5, 37.1, 32.5, 31.5, 28.4, 27.0, 26.4, 26.1, 26.0, 25.8, 24.3, 23.2, 20.9, 18.4, 18.2, 16.4, 15.5, −4.3, −5.0, −5.1 and −5.5; high resolution mass spectrum (CI, ammonia) *m/z* 609.4421 [$(M + H)^+$; Calc. for $C_{34}H_{65}O_5Si_2$: 609.4373] (Found: C, 66.95; H, 10.6. Calc. for $C_{34}H_{64}O_5Si_2$: C, 67.06; H, 10.60%).

Aphidicolin 17-*Acetate* **26**.—A solution of **25** (15 mg, 0.025 mmol) in methylene dichloride (0.25 ml) and acetonitrile (0.50 ml) was cooled to −5 °C and 1 drop of 48% hydrofluoric acid was added. The reaction mixture was stirred at −5 °C for 5 min and at room temperature for 15 min, and then subjected to work-up as described for the preparation of **1** from **24**. Preparative TLC, with 75% ethyl acetate and 2% methanol in hexanes as eluent, gave **26** (8 mg, 86%) as colourless needles, m.p. 191.5–195.5 °C (lit.,[1b,3,3] 193.5–196 °C); $[\alpha]_D^{20}$ 4.0° (*c* 0.05, methanol); $\nu_{max}(CHCl_3)/cm^{-1}$ 3350br,s, 2960s, 2940s, 2850m, 1750s, 1380m, 1275m, 1230s, 1040s and 1025m; δ_H(500 MHz, $CDCl_3$) 3.97 (ABq, J_{ab} 11.4, $\Delta\nu_{ab}$ 22.8, 2 H), 3.69 (s, 1 H), 3.50–3.45 (m, 2 H), 3.37 (d, *J* 9.8, 1 H), 3.11 (d, *J* 8.5, 1 H), 2.42 (dd, *J* 12.6 and 3.3, 1 H), 2.12 (d, *J* 6.4, 1 H), 2.10 (s, 3 H), 2.06–1.95 (m, 5 H), 1.91–1.77 (m, 3 H), 1.71–1.68 (m, 1 H), 1.56–1.46 (m, 4 H), 1.39–1.30 (m, 3 H), 1.29–1.22 (m, 1 H), 1.02–0.94 (m, 1 H), 0.98 (s, 3 H) and 0.71 (s, 3 H); δ_C(125 MHz, $CDCl_3$) 171.2, 73.5, 71.8, 69.9, 48.9, 41.6, 40.6, 39.9, 39.7, 33.4, 32.5, 31.5, 28.3, 27.3, 26.8, 26.4, 24.5, 23.0, 20.9, 17.9 and 15.0; high resolution mass

spectrum (CI, ammonia) m/z 298.2880 [$(M + NH_4)^+$; Calc. for $C_{22}H_{40}NO_5$: 398.2906].

Methyl 3α,18-*Dihydroxyaphidicol*-15-*ene*-16-*carboxylate* **28**.—A stirred mixture of isopropylidene ester **19a** (40 mg, 0.103 mmol), BIO-RAD AG50W-X_2 50–100 mesh H^+ ion exchange resin (15 mg) and methanol (1 ml) was heated at reflux for 30 min, cooled to room temperature and then filtered through a pad of Celite. The filtrate was evaporated and the resulting white solid recrystallized from ether–hexanes to give the ester **28** (33 mg, 92%), m.p. 144.5–146 °C; $[\alpha]_D^{20} = -8.83$ (c 0.30, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3610w, 3480m, 3000m, 2940s, 2870m, 1700s, 1650m, 1440m, 1380m, 1210m, 1200s, 1185m and 1080s; δ_H(500 MHz, $CDCl_3$) 6.68 (s, 1 H), 3.71 (s, 1 H), 3.58–3.48 (m, 2 H), 3.37 (d, J 10.7, 1 H), 3.00–2.95 (m, 2 H), 2.61 (ABX, J_{ab} 20.6, J_{ax} 4.2, J_{bx} 3.0, 2 H), 2.25 (dd, J 12.5 and 2.5, 1 H), 2.17–2.03 (m, 3 H), 1.94 (dd, J 14.3 and 12.3, 1 H), 1.71–1.63 (m, 2 H), 1.54–1.48 (m, 3 H), 1.38–1.33 (m, 1 H), 1.21 (d, J 10.7, 1 H), 1.07 (s, 3 H), 1.02–0.95 (m, 2 H) and 0.71 (s, 3 H); δ_C(125 MHz, $CDCl_3$) 166.7, 142.8, 139.4, 71.5, 51.4, 48.9, 42.1, 40.1, 39.4, 39.1, 35.5, 32.8, 31.9, 29.2, 26.7, 26.2, 25.2, 21.9, 17.5 and 16.1; high resolution mass spectrum (CI, ammonia) m/z 349.2350 [$(M + H)^+$; Calc. for $C_{21}H_{33}O_4$: 349.2379].

Methyl 15β,16β-*Epoxy*-3α,18-*dihydroxyaphidicolane*-16α-*carboxylate* **29**.—A stirred mixture of the isopropylidene epoxy ester **20a** (25 mg, 0.062 mmol), BIO-RAD AG50W-X_2 50–100 mesh H^+ ion exchange resin (15 mg) and methanol (1 ml) was heated at reflux for 30 min, cooled to room temperature, and then filtered through a pad of Celite. The filtrate was evaporated and the resulting white solid recrystallized from hot ethyl acetate to give the diol **29** (19 mg, 84%), m.p. 214–216 °C; $[\alpha]_D^{20}$ 25° (c 0.3, MeOH); ν_{max}(KBr)/cm^{-1} 3350br,s, 2960s, 2850m, 1740s, 1430m, 1260s and 1035s; δ_H(500 MHz, $CDCl_3$) 3.74 (br s, 1 H), 3.50–3.43 (m, 2 H), 3.38–3.34 (m, 2 H), 3.18 (dd, J 9.0 and 2.7, 1 H), 2.75 (t, J 6.6, 1 H), 2.36 (d, J 16.4, 1 H), 2.22–2.19 (m, 1 H), 2.16–2.08 (m, 3 H), 2.06–1.92 (m, 2 H), 1.74–1.71 (m, 1 H), 1.67 (d, J 11.5, 1 H), 1.54–1.40 (m, 3 H), 1.33–1.24 (m, 2 H), 1.11 (dd, J 13.2 and 10.1, 1 H), 0.99–0.95 (m, 1 H), 0.95 (s, 3 H) and 0.68 (s, 3 H); δ_C(125 MHz, $CDCl_3$) 171.0, 72.2, 71.6, 62.1, 57.2, 52.5, 47.7, 40.9, 40.3, 39.4, 33.9, 33.2, 32.3, 29.2, 26.9, 26.2, 26.1, 24.5, 21.8, 17.5 and 15.0; high resolution mass spectrum (CI ammonia) m/z 382.2594 [$(M + NH_4)^+$; Calc. for $C_{21}H_{36}NO_5$: 382.2593].

Acknowledgements

Support for this investigation was provided by the National Institutes of Health (National Cancer Institute) through grant CA-22807 and by Merck Sharp and Dohme Research Laboratories. ICI Pharmaceuticals Division is gratefully acknowledged for a generous gift of natural aphidicolin. The authors also wish to thank Dr. Katsumi Fujimoto for investigation of the Sharpless osmylation reaction and Dr. Christopher S. Shiner for helpful suggestions and critical comments.

References

1 (*a*) K. M. Brundret, W. Dalziel, B. Hesp, J. A. J. Jarvis and S. Neidle, *J. Chem. Soc., Chem. Commun.*, 1972, 1027; (*b*) W. Dalziel, B. Hesp, K. M. Stevenson and J. A. J. Jarvis, *J. Chem. Soc., Perkin Trans. 1*, 1973, 2841.

2 R. A. Bucknall, J. Moores, R. Simms and B. Hesp, *Antimicrob. Agents Chemother.*, 1973, **4**, 294.

3 (*a*) S. Spadari, F. Focher, C. Kuenzle, E. J. Corey, A. G. Meyers, N. Hardt, A. Rebuizzini, G. Ciarroccho and G. Pedrali-Noy, *Antiviral Res.*, 1985, **5**, 93; (*b*) G. Pedrali-Noy, G. Mazza, F. Focher and S. Spadari, *Biochem. Biophys. Res. Commun.*, 1980, **93**, 1094.

4 (*a*) S. Ikegami, T. Taguchi, M. Ohashi, M. Oguro, H. Nagano and Y. Mano, *Nature (London)*, 1978, **275**, 458. For reviews of the biological activity of aphidicolin, see: (*b*) J. A. Huberman, *Cell*, 1981, **23**, 647; (*c*) S. Spadari, F. Sala and G. Pedrali-Noy, *Trends Biochem. Sci.*, 1982, **7**, 29.

5 (*a*) M. R. Adams and J. D. Bu'Lock, *J. Chem. Soc., Chem. Commun.*, 1975, 389; (*b*) M. J. Ackland, J. R. Hanson, A. H. Ratcliffe and I. H. Sadler, *J. Chem. Soc., Chem. Commun.*, 1982, 165; (*c*) M. J. Ackland, J. R. Hanson and A. H. Ratcliffe, *J. Chem. Soc., Perkin Trans. 1*, 1984, 2751; (*d*) M. J. Ackland, J. R. Hanson, B. L. Yeoh and A. H. Ratcliffe, *J. Chem. Soc., Perkin Trans. 1*, 1985, 2705; (*e*) M. J. Ackland, J. F. Gordon, J. R. Hanson, B. L. Yeoh and A. H. Ratcliffe, *J. Chem. Soc., Chem. Commun.*, 1987, 1492; (*f*) M. J. Ackland, J. Gordon, J. R. Hanson, B. L. Yeoh and A. H. Ratcliffe, *J. Chem. Soc., Perkin Trans. 1*, 1988, 1477; (*g*) M. J. Ackland, J. F. Gordon, J. R. Hanson and A. H. Ratcliffe, *J. Chem. Soc., Perkin Trans. 1*, 1988, 2009; (*h*) J. F. Gordon, J. R. Hanson and A. H. Ratcliffe, *J. Chem. Soc., Chem. Commun.*, 1988, 6; (*i*) M. J. Ackland, J. Gordon, J. R. Hanson, B. L. Yeoh and A. H. Ratcliffe, *Phytochemistry*, 1988, **27**, 1031.

6 B. M. Trost, Y. Nagetoshi, K. Yamamoto and S. S. McElvain, *J. Am. Chem. Soc.*, 1979, **101**, 1328.

7 (*a*) J. E. McMurry, A. Andrus, G. M. Ksander, J. H. Musser and M. A. Johnson, *J. Am. Chem. Soc.*, 1979, **101**, 1330; (*b*) J. E. McMurry, A. Andrus, G. M. Ksander, J. H. Musser and M. A. Johnson, *Tetrahedron, Suppl. 9*, 1981, **37**, 319.

8 E. J. Corey, M. Tius and J. Das, *J. Am. Chem. Soc.*, 1980, **102**, 1742.

9 (*a*) R. E. Ireland, J. D. Godfrey and S. Thaisrivongs, *J. Am. Chem. Soc.*, 1981, **103**, 2446; (*b*) R. E. Ireland, W. C. Dow, J. D. Godfrey and S. Thaisrivongs, *J. Org. Chem.*, 1984, **49**, 1001.

10 E. E. van Tamelen, S. R. Zawacky, R. K. Russell and J. G. Carlson, *J. Am. Chem. Soc.*, 1983, **105**, 142.

11 (*a*) R. M. Bettolo, P. Tagliatesta, A. Lupi and D. Bravetti, *Helv. Chim. Acta*, 1983, **66**, 1922; (*b*) A. Lupi, M. Patamia and R. M. Bettolo, *Helv. Chim. Acta*, 1988, **71**, 872.

12 R. A. Holton, R. M. Kennedy, H. B. Kim and M. E. Krafft, *J. Am. Chem. Soc.*, 1987, **109**, 1597.

13 C. Iwata, T. Kuroda, K. Murakami, T. Inoue, T. Imanishi and T. Tanaka, personal communication.

14 (*a*) S. P. Tanis, Y. H. Chuang and D. B. Head, *Tetrahedron Lett.*, 1985, **26**, 2833; (*b*) S. P. Tanis, Y. H. Chuang and D. B. Head, *J. Org. Chem.*, 1988, **53**, 4929.

15 (*a*) P. K. Ghosal, D. Mukherjee and P. C. Dutta, *Tetrahedron Lett.*, 1976, 2997; (*b*) S. K. Maity, B. Basu and D. Mukherjee, *Tetrahedron Lett.*, 1983, **24**, 3921; (*c*) S. K. Maity and D. Mukherjee, *Tetrahedron Lett.*, 1983, **24**, 5919; (*d*) S. K. Maity and D. Mukherjee, *Tetrahedron*, 1984, **40**, 757; (*e*) T. Kametani, T. Honda, Y. Shiratori and K. Fukumoto, *Tetrahedron Lett.*, 1980, **21**, 1665; (*f*) T. Kametani, T. Honda, Y. Shiratori, H. Matsumoto and K. Fukumoto, *J. Chem. Soc., Perkin Trans. 1*, 1981, 1386; (*g*) R. L. Cargill, D. F. Bushey, J. R. Dalton, R. S. Prasad, R. D. Dyer and J. Bordner, *J. Org. Chem.*, 1981, **46**, 3389; (*h*) K. C. Nicolaou and R. E. Zipkin, *Angew. Chem., Int. Ed. Engl.*, 1981, **20**, 785; (*i*) G. A. Mock, A. B. Holmes and R. A. Raphael, *Tetrahedron Lett.*, 1977, 4539; (*j*) V. L. Bell, A. B. Holmes, S. Y. Hsu, G. A. Mock and R. A. Raphael, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1507; (*k*) V. L. Bell, P. J. Gidding, A. B. Holmes, G. A. Mock and R. A. Raphael, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1515; (*l*) C. Iwata, T. Morie and T. Tanaka, *Chem. Pharm. Bull.*, 1985, **33**, 944; (*m*) C. Iwata, T. Morie, N. Maezaki, H. Shimamura, T. Tanaka and T. Imanishi, *J. Chem. Soc., Chem. Commun.*, 1984, 930; (*n*) A. J. Pearson, G. C. Heywood and M. Chandler, *J. Chem. Soc., Perkin Trans. 1*, 1982, 2631; (*o*) A. J. Pearson and M. K. O'Brien, *Tetrahedron Lett.*, 1988, **29**, 869; (*p*) M. M. Abelman and L. E. Overman, *J. Am. Chem. Soc.*, 1988, **110**, 2328.

16 H. Koyama, O. Hideke, S. Kobayashi and M. Ohno, *Tetrahedron Lett.*, 1985, **22**, 2685.

17 For a preliminary communication, see: C. J. Rizzo and A. B. Smith, III, *Tetrahedron Lett.*, 1988, **29**, 2793; (*b*) for part 2 in this series, see: C. J. Rizzo, J. L. Wood, G. T. Furst and A. B. Smith, III, *J. Nat. Prod.*, 1990, **53**, 735.

18 E. E. van Tamelen, J. G. Carlson, R. K. Russell and S. R. Zawacky, *J. Am. Chem. Soc.*, 1981, **103**, 4615.

19 (*a*) E. N. Jacobsen, I. Marko, W. S. Mongall, G. Schroder and K. B. Sharpless, *J. Am. Chem. Soc.*, 1988, **110**, 1968; (*b*) J. S. M. Wai, I. Marko, J. S. Svendsen, M. G. Fin, E. N. Jacobsen and K. B. Sharpless, *J. Am. Chem. Soc.*, 1989, **111**, 1123.

20 F. A. Davis and S. Chattopadhyay, *Tetrahedron Lett.*, 1986, **27**, 5079.

21 S. Masamune, W. Choy, J. S. Petersen and L. R. Sita, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 1.

22 K. Fujimoto, C. J. Rizzo and A. B. Smith, III, unpublished results.
23 (*a*) R. R. Sauers, H. M. How and H. Feilich, *Tetrahedron*, 1965, **21**, 983; (*b*) R. B. Kelly, M. L. Harley, S. J. Alward and P. S. Manchand, *Can. J. Chem.*, 1982, **60**, 675.
24 A. Yasuda, H. Yamamoto and H. Nozaki, *Bull. Chem. Soc. Jpn.*, 1979, **52**, 1705.
25 S. Murata, M. Suzuki and R. Noyori, *J. Am. Chem. Soc.*, 1979, **101**, 2738.
26 S. Cacchi, E. Morera and G. Ortar, *Tetrahedron Lett.*, 1985, **26**, 1109.
27 P. A. Wender and S. L. Eck, *Tetrahedron Lett.*, 1982, **23**, 1871.
28 (*a*) P. J. Stang and W. Treptow, *Synthesis*, 1980, 283; (*b*) M. E. Wright and S. R. Pulley, *J. Org. Chem.*, 1989, **54**, 2886.
29 Y. Kishi, M. Aratani, H. Tanino, T. Fukuyama and T. Goto, *J. Chem. Soc., Chem. Commun.*, 1972, 64.
30 W. H. Rastetter, T. J. Richards and M. D. Lewis, *J. Org. Chem.*, 1972, **43**, 3163.
31 (*a*) J. E. McMurry and T. R. Webb, *J. Med. Chem.*, 1984, **27**, 1367; (*b*) S. Hiranuma, T. Shimizu, H. Yoshioka, K. Ono, H. Nakane and T. Takahashi, *Chem. Pharm. Bull.*, 1987, **35**, 1641.
32 (*a*) J. Ipsen, J. Fuska, A. Foskova and J. P. Rosazza, *J. Org. Chem.*, 1982, **47**, 3278; (*b*) J. Ipsen and J. P. Rosazza, *J. Nat. Prod.*, 1984, **47**, 497.
33 A. Ichihara, H. Oikawa, K. Hayashi, M. Hashimoto, S. Sakamura and R. Sakai, *Agric. Biol. Chem.*, 1984, **48**, 1687.
34 T. Haraguchi, M. Oguro, H. Nagano, A. Ichihara and S. Sakamura, *Nucleic Acids Res.*, 1983, **11**, 1197.
35 P. J. O'Dwyer, J. D. Moter, M. Suffness and J. Plowman, *Proceedings of the 76th Annual Meeting of the American Association for Cancer Research*; May 22–25, 1982, Houston TX; Abstr. 1009.
36 Personal communication: Dr. A. H. Todd, Development Department, ICI Pharmaceuticals Division and Dr. G. F. Costello of ICI Development Division.
37 (*a*) R. F. Newton, D. P. Reynolds, M. A. W. Finch, D. R. Kelly and S. M. Roberts, *Tetrahedron Lett.*, 1979, 3981; (*b*) R. J. Batten, A. J. Dixon, R. J. K. Taylor and R. F. Newton, *Synthesis*, 1980, 234.
38 J. E. McMurry and T. R. Webb, *J. Med. Chem.*, 1984, **27**, 1367, and references cited therein.
39 S. Hiranuma, T. Shimizu, H. Yoshioka, K. Ono, H. Nakane and T. Takahashi, *Chem. Pharm. Bull.*, 1987, **35**, 1641.

Paper 0/05529H
Received 10*th December* 1990
Accepted 19*th December* 1990