Isosteres of the DNA Polymerase Inhibitor Aphidicolin as Potential Antiviral Agents against Human Herpes Viruses†

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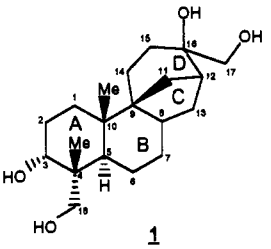
A variety of isosteres of the DNA polymerase inhibitor aphidicolin were synthesized as potential antiherpes agents. Modeling studies indicated that the bicyclooctane C, D rings of aphidicolin could be replaced by an aromatic moiety while maintaining the spatial arrangement of the hydroxyl group equivalent to the essential C18 hydroxyl group of aphidicolin. Of the racemic isosteres synthesized only **13**, the compound with the greatest structural similarity to aphidicolin, showed any significant antiviral activity in primary assays. An enantioselective synthesis of the compound was carried out and the 4a*S* isomer **36** was shown to account for the observed antiviral activity noted against herpes simplex virus 1 and human cytomegalovirus.

Introduction

Aphidicolin, **1**, a diterpene antibiotic isolated from the fungus *Cephalosporium aphidicola*,[1] is a potent inhibitor of eukaryotic DNA polymerases including mammalian DNA polymerase α and herpes viral DNA polymerases,[2,3] indeed, aphidicolin is used routinely to characterize newly isolated enzymes.[4] We were interested in the activity of aphidicolin against the herpes DNA polymerases, especially that of human cytomegalovirus (HCMV).[5] HCMV is known to lack a thymidine kinase enzyme and thus is resistant to most conventional nucleoside antiviral agents which require metabolic activation to their triphosphates. Nucleosides which have anti-HCMV activity such as ganciclovir are believed to be phosphorylated by a protein kinase like enzyme.[6] Aphidicolin does not require any metabolic activation for its DNA polymerase inhibitory activity and therefore constitutes an attractive lead for developing an antiviral agent against HCMV as well as the other herpes viruses. Aphidicolin itself shows no selectivity for the viral over the mammalian polymerases and thus exhibits cell toxicity *in vitro*. It is therefore not a useful antiviral agent. We decided to modify the aphidicolin structure to search for simpler isosteric compounds with selectivity for the viral enzymes.

Aphidicolin is a competitive inhibitor for 2′-deoxycytosinetriphosphate (dCTP) at the active site of the enzyme. Support for an interaction with the nucleotide binding site is provided by sequence analysis of HSV polymerase mutants. Mutations which show altered drug sensitivity to nucleoside analogs and the pyrophosphate drugs also show altered sensitivity to aphidicolin.[3] Despite this and in common with other workers,[7] we could not form convincing overlays of the aphidicolin structure with dCTP. In the design of our novel putative inhibitors, we utilized the available structure–activity relationship (SAR) data on semisynthetic derivatives of the natural product against DNA polymerase α together with computer graphics in order to determine suitable synthetically



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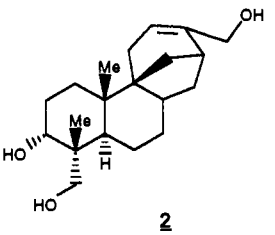

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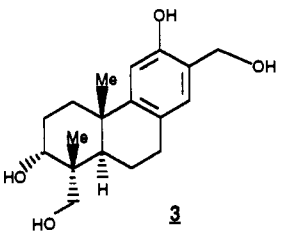

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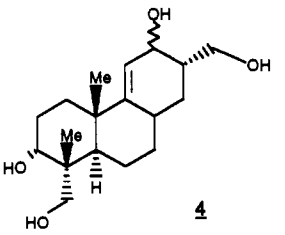

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accessible structures. Unfortunately SAR data concerning aphidicolin derivatives and viral DNA polymerases was not available; however, DNA polymerase α shows marked similarities with the viral polymerases both in terms of primary structure[8] and drug sensitivity,[3] and this information therefore served as a useful starting point.

Briefly summarizing the published SAR data,[7,9,10] it seems clear that the C18 hydroxyl is essential for high activity; loss of the C3 hydroxyl diminishes but does not abolish activity, though the A ring of aphidicolin is highly sensitive to most other structural modifications. In contrast the precise position and orientation of hydroxyl groups in the D ring seem to allow scope for structural modification in this region of the molecule. For example the 15-ene derivative **2** was reported[9] as having DNA polymerase α inhibitory activity. In the design of simpler analogs therefore, we determined to maintain the structure of the A ring but modify the molecule in the region of the C and D rings, thus eliminating a layer of chemical complexity. Polyhydrophenanthrene structures such as **3** and **4** formed excellent overlays with the aphidicolin structure. In the case of **3** (Figure 1), the A and B rings were almost superimposable whereas the aromatic C ring fitted through the bicyclooctane ring system of aphidicolin

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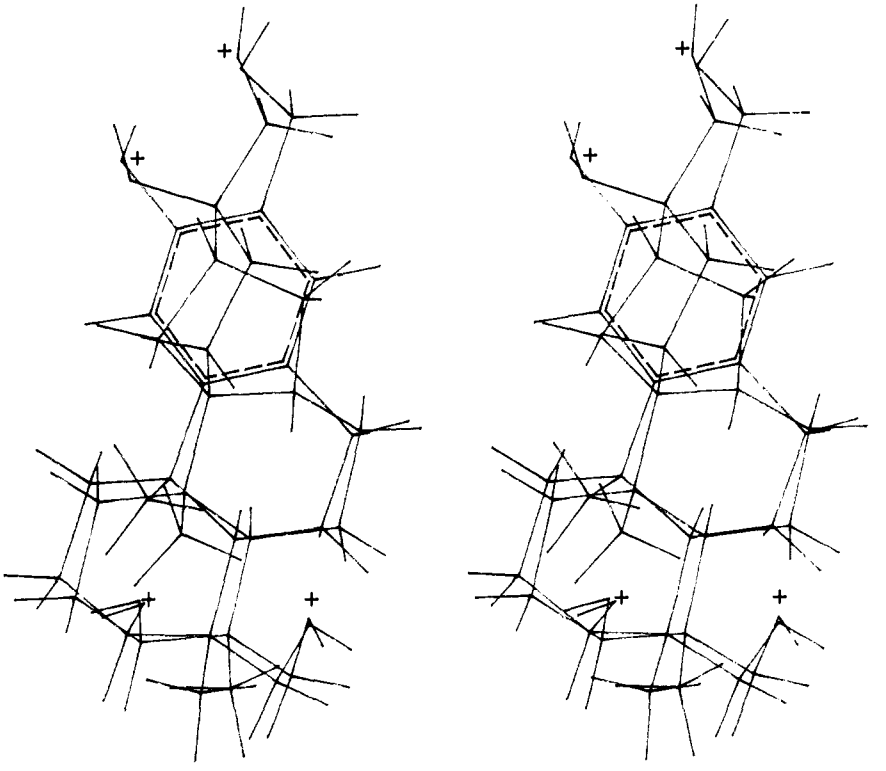
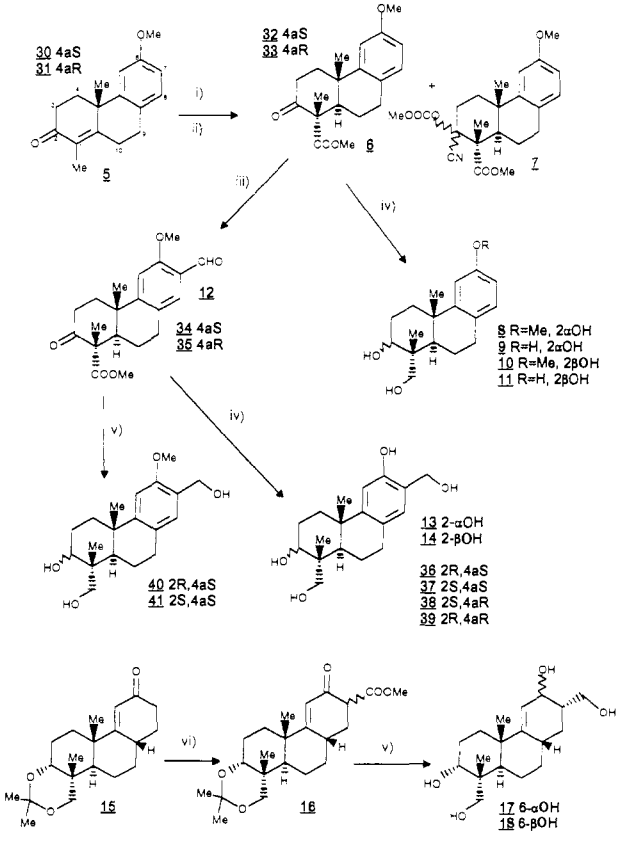


Figure 1. Stereoview of overlay of aphidicolin **1** with structure **3**.

Scheme I. Synthesis of 3-Hydroxylated Analogues of Aphidicolin[a]



[a] Reagents: (i) Li/NH_3; (ii) MeOOCCN; (iii) $TiCl_4/Cl_2CHOCH_3$; (iv) DIBAlH/reflux; (v) DIBAlH/0 °C; (vi) LDA/MeOOCCN. For reasons of economy of space, all structures are drawn as the 4aS series. Enantiomeric pairs are labeled as shown; all other compounds are racemic.

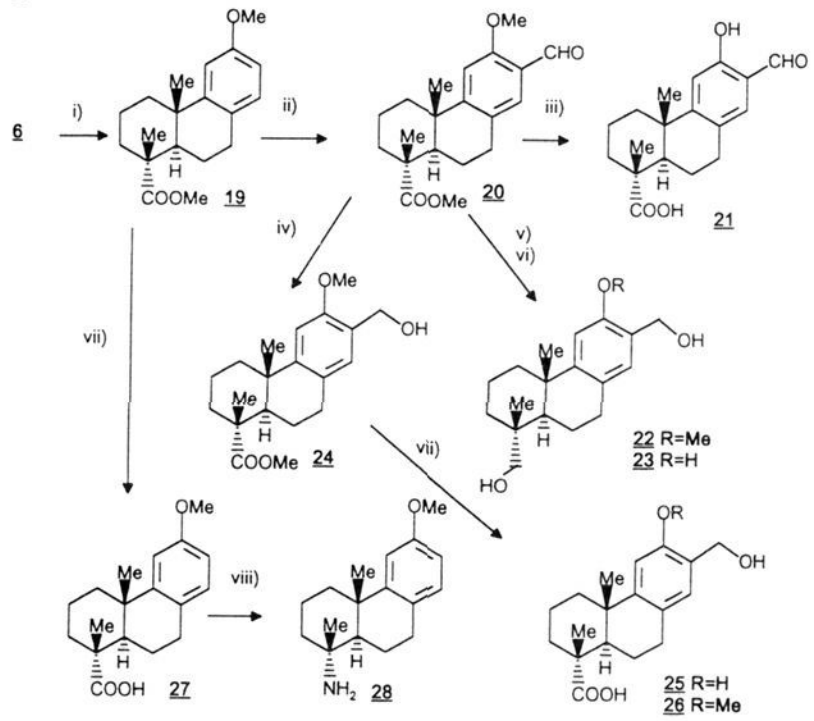
to position the C18 and C17 hydroxyl equivalents close to their positions in aphidicolin. The reduced compound **4** showed a similar close overlay (not shown). The task remained to synthesize these derivatives and similar analogs and assay their antiviral and DNA polymerase activity.

Chemistry

The total synthesis of aphidicolin has been completed by several different groups, and much innovative and elegant chemistry has been reported.[11] Synthetic derivatives required for biosynthetic studies have also been reported.[12] The principal complexity is involved in the construction of the bicyclooctane moiety. Our simpler isosteres allowed the construction of a variety of structures, though the chemistry involved was still multistage and sometimes problematic.

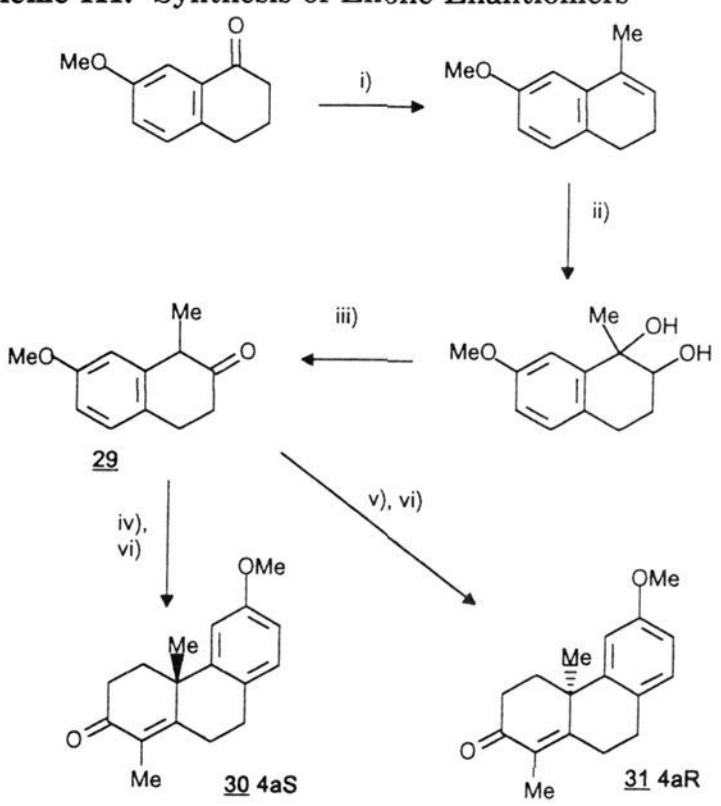
Our chief starting point for the work was the known racemic enone[13] **5** (Scheme I) which was converted into the key keto-ester intermediate **6** by generation of the specific lithium enolate using lithium ammonia reduction and trapping with methyl cyanoformate.[14] This represents an improvement in convenience over the previously reported method involving the use of solid carbon dioxide and subsequent methylation.[15] Small amounts of the acylated cyanohydrin **7** were also isolated which could be hydrolyzed to **6**. We also obtained impure products consistent with O rather than C acylation. Similar results were reported by Mander.[14] In later work[16] on related systems, we showed that the use of toluene as solvent rather than THF increased the proportion of C acylation. Reaction of the keto-ester **6** with DIBALH[17] at reflux gave reduction of the keto-ester functionality with simultaneous demethylation to provide the target diols **8–11**. Formylation of **6** in the C ring by treatment with titanium tetrachloride/dichloromethyl methyl ether and similar treatment with DIBALH gave the hydroxymethylated versions **13** and **14**, now bearing hydroxyl groups equivalent to the essential 17-hydroxyl of aphidicolin.

Scheme II. Synthesis of 3-Deoxo Analogues of Aphidicolin[a]



[a] Reagents: (i) $PhNHNH_2/NaCNBH_4$; (ii) $TiCl_4/Cl_2CH_2OCH_3$; (iii) NaSEt/DMF; (iv) $LiBH_4$/0 °C; (v) $LiBH_4$/room temperature for **22**; (vi) DIBAlH/reflux for **23**; (vii) *p*-NaSPhMe/DMF extended reflux for **25**; (viii) DPPA/BuOH. All compounds are racemic.

Scheme III. Synthesis of Enone Enantiomers[a]



[a] Reagents: (i) $MeMgBr/H_3O^+$; (ii) OsO_4/NMNMO; (iii) *p*-TsOH; (iv) (*R*)-(+)-$H_2NCHMePh$/*p*-TsOH; (v) (*S*)-(−)-$H_2NCHMePh$/*p*-TsOH; (vi) NaOMe/MeOH.

Specific enolate generation and acylation was again employed in the synthesis of the tetrols **17** and **18** from the known enone **15**,[18] though in this case the DIBALH reduction gave poor yields of the tetrols.

Scheme II shows the synthesis of some 3-deoxo isosteres of aphidicolin. Removal of the sensitive keto–ester functionality gave a more durable molecule and allowed greater structural modifications to be carried out; acid (**21**, **25**, **26**, and **27**) and amino functions **28** were introduced at the equivalent of C4. The 3-deoxo versions of **13** and **14** were also synthesized. The synthesis of the amine **28** is noteworthy in that the tertiary amine is introduced stereoselectively using diphenyl phosphorodiazidate.[19] All structures **5**–**29** in Schemes I–III are racemic compounds and the structures indicate relative stereochemistry only. Structures **30**–**41** are pure enantiomers.

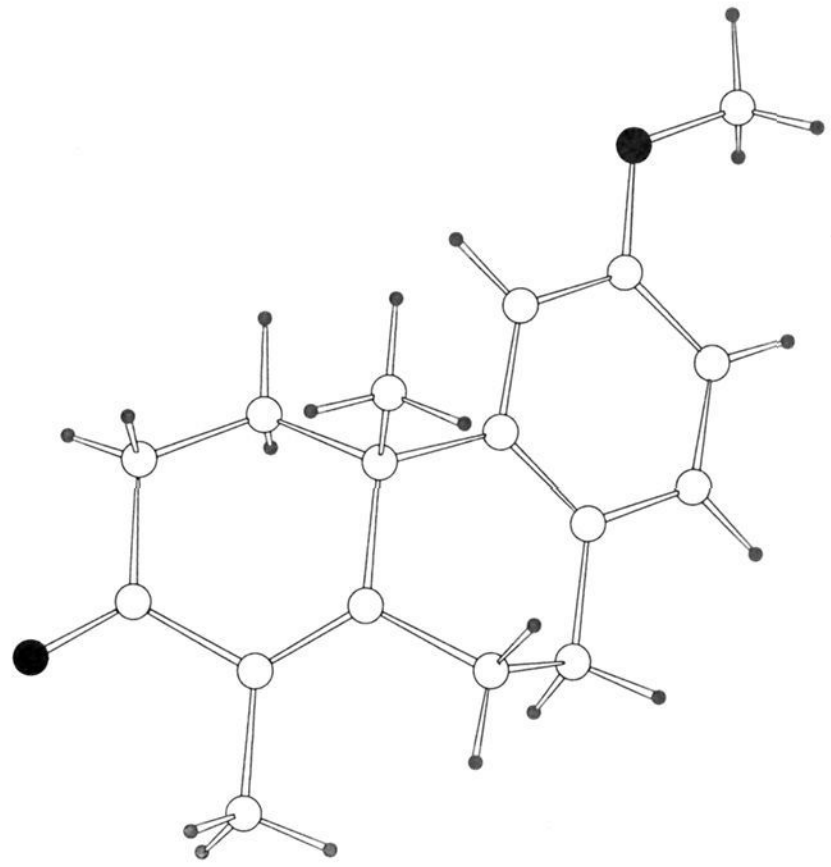


Figure 2. X-ray crystal structure of 4a*S* enone **30**.

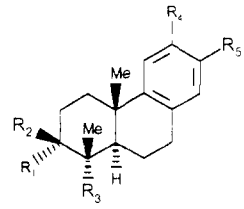
Enantioselective Syntheses

In order to synthesize the enantiomers of the tetrol **13** we required the 4a*S* and 4a*R* enones **30** and **31** (Scheme III). These compounds proved surprisingly easy to synthesize from the readily available, though unstable, tetralone **29**. The tetralone was synthesized by the short sequence shown in Scheme III in which the large-scale (90 g) diol formation with *N*-methylmorpholine *N*-oxide and catalytic osmium tetraoxide[20] was the key transformation. The intermediate diol was not isolated but rearranged directly into the tetralone **29**. Modification of d'Angelos method[21] using *R*-(+) or *S*-(−)-α-methylbenzylamine as the chiral auxiliary gave the 4a*S* (**30**) and 4a*R* (**31**) enones, respectively. A single crystallization of the crude enones provided material of >96% (**30**) and >97% (**31**) ee, determined by NMR studies using the tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium-(III) [Eu(thc)$_3$] chiral shift reagent. CD spectra of the enantiomers were mirror images. In order to confirm our stereochemical assignments we performed an X-ray on the 4a*S* enone **30** (Figure 2) which showed the expected stereochemistry at the chiral center. The synthesis of the enantiomers of the triols **13** and **14**, i.e. **36**–**39** was then carried out by repeating the chemistry shown in Scheme I (for convenience the 4a*S* series only is shown in the scheme).

Molecular Modeling

Molecular modeling was carried out using the graphics software SYBYL (TRIPOS Inc.). A model for aphidicolin **1** was constructed using visual reference to the published structural diagram from X-ray crystallography of the related bis-acetonide[22] for initial modeling of the heavy atoms. H atoms were added and their positions optimized through the energy minimization routine MAXIMIN2. Molecule **3** was built through retrieval of a related structure DOWDIC from the Cambridge Crystallographic Database,[23,24] modeling of the additional groups, and an energy optimization similar to that for **1**. The molecules were initially overlaid using their common cyclohexyl moieties (A ring of **1**). The conformations of the two hydroxymethyl

Table I. Results of Primary Assays of Racemic Aphidicolin Analogs



compound	R_1	R_2	R_3	R_4	R_5	HSV2[a] in vero cells	DNA polymerase α	HSV2 DNA polymerase
aphidicolin, 1							2[b]	5[b]
8	OH	H	CH_2OH	OMe	H	36	0	nd
9	OH	H	CH_2OH	OH	H	25	8	nd
10	H	OH	CH_2OH	OMe	H	10	0	nd
11	H	OH	CH_2OH	OH	H	34	0	0
13	OH	H	CH_2OH	OH	CH_2OH	90	4	0
14	H	OH	CH_2OH	OH	CH_2OH	19	7	0
20	H	H	COOMe	OMe	CHO	T100	2	0
21	H	H	COOH	OH	CHO	0	5	0
22	H	H	CH_2OH	OMe	CH_2OH	T100	3	0
23	H	H	CH_2OH	OH	CH_2OH	0	0	nd
24	H	H	COOMe	OMe	CH_2OH	T100	0	0
25	H	H	COOH	OH	CH_2OH	15	0	0
26	H	H	COOH	OMe	CH_2OH	13	0	0
27	H	H	COOH	OMe	H	31	4	0
28	H	H	NH_2	OMe	H	T100	1	0
17						0	nd	nd

[a] All figures are quoted as percent inhibition at 100 μM. [b] EC50 value in μM. T = toxicity observed in cell line; nd = not determined.

Table II. Evaluation of Enantiomeric Pairs against Herpes Viruses[a]

compound	HSV1 in vero cells	HSV2 in vero cells	HCMV in MRC5 cells	VZV in MRC5 cells	vero cells cytotoxicity
36 4a*S*	133	≫100	76	≫100	>500
38 4a*R*	>200	≫100	≫100	≫100	>500
37 4a*S*	198	≫100	≫100	≫100	>500
39 4a*R*	222	≫100	≫100	≫100	>500
40 4a*S*	≫100	≫100	≫100	≫100	>500
41 4a*S*	≫100	≫100	≫100	≫100	>500

[a] Values are IC50's in μM.

groups of each were then adjusted to approximate coincidence and a subsequent overlay using only the four oxygen atoms as targets (Figure 1) gave an RMS fit of 0.038 nm.

Antiviral and Enzyme Assays

Herpes antiviral screening was carried out as described by Purifoy.[25] Herpes simplex virus 2 (HSV2) DNA polymerase assays were performed as described by Powell.[26] HCMV and DNA polymerase α assays were performed as described by Ertl[27] using activated calf thymus DNA as the DNA template but with no added salt (NaCl or KCl).

Results and Discussion

Initially we tested the compounds in a plaque reduction assay against HSV2 and also in enzyme assays against DNA α polymerase and HSV2 polymerase. Of the racemic compounds 8–14 only 13, i.e. one of the compounds with the greatest structural similarity to aphidicolin, showed any significant activity in our primary assays (see Table I), although 13 showed no activity in the polymerase assays. All of our 3-deoxo analogs 20–28 were inactive, as were the reduced compounds 17 and 18.

The results for 13 indicated some activity against the live virus so we resolved to synthesize the enantiomers of 13 as described above in order to obtain definitive data. The results, shown in Table II indicated fairly weak antiviral activity, though 36, the compound with aphidicolin-like absolute stereochemistry did have HSV1 activity (133 μM) and HCMV activity (76 μM) with none being observed for its antipode 38. None of the other enantiomerically pure compounds synthesized (37, 39–41) had any significant antiviral or DNA polymerase α, or HSV2 polymerase activity. Compound 36 was also evaluated against HCMV DNA polymerase[27] but showed no inhibition at 100 μM compared to 85% at 100 μM for aphidicolin in the same assay. It is therefore unclear whether the antiviral activity of 36 (and 13) represents an action on the viral polymerases; however, the close structural similarity of 36 to aphidicolin and the lack of activity for all the other analogs still makes such a conclusion tempting.

The reasons for the weak activity of these compounds are not immediately apparent. The analogs were designed such that the structural variations were carried out at the least sensitive end of the molecule. Of course our simple analogs do not position the hydrogen bonding groups at precisely the same locations as in aphidicolin; however, excellent overlays of the four hydroxyl groups with aphidicolin were observed. If the aromatic moiety could not be accommodated at the active site, then the reduced analogs 17 and 18 might have been expected to show better activity. The most obvious lack in our analogs would appear to be any lipophilic interaction derived from the bicyclooctane C and D rings of aphidicolin. Interestingly a Japanese patent[28] has recently claimed antitumour activity for the 17-amino derivatives of aphidicolin, though no information on DNA polymerase α activity was given.

We have shown that the aphidicolin structure is exceptionally sensitive to variations, largely confirming the data obtained by other workers on semisynthetic derivatives of aphidicolin. If aphidicolin binds at the dCTP active site, then it at least shares its high degree of specificity with the 2′-deoxynucleosidetriphosphates (dNTP's) which it apparently mimics. An X-ray structure of aphidicolin bound at the polymerase active site would have been very useful for this study; however, the only X-ray available for a DNA polymerase is a relatively

unrefined one on the *E. coli* Klenow fragment,[29] and this prokaryotic enzyme is insensitive to aphidicolin. Although much progress has been made in recent years on obtaining non-NTP inhibitors of reverse transcriptases,[30] little corresponding progress has been made for DNA polymerases. Some diterpenes related to aphidicolin, i.e. scopadulcic acids,[31] were reported as having antiviral activity though their DNA polymerase activity (if any) was not given. It seems reasonable to suppose that selective non-nucleoside inhibitors of viral DNA polymerases will eventually emerge and expand the range and selectivity of antiherpes agents.

Experimental Section

Melting points are uncorrected. Flash chromatography was carried out by the method of Still[32] except that the columns were slurry packed. Merck silica art. no. 9385 was used. The CD spectra of the compounds, as ~50 μM ethanol solutions were acquired on a JASCO J600 spectrometer. NMR spectra were run on a Bruker spectrometer at 200 MHz unless otherwise indicated. Chemical shifts are in δ ppm relative to TMS.

1,4a-Dimethyl-6-methoxy-1,4,4a,9,10,10a-hexahydro-2-oxophenanthrene-1-carboxylic Acid, Methyl Ester (6) and 2-(carbomethoxyoxy)-2-cyano-1β,4aβ-dimethyl-6-methoxy-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-1α-carboxylic acid, Methyl Ester (7). Lithium wire (0.84 g, 120 mmol), cut into 1-cm lengths, was added to liquid ammonia (500 mL), at −50 °C, and the mixture was stirred for 15 min. To the blue solution was added tetrahydrofuran (75 mL) followed by **5** (15.36 g, 60 mmol) in tetrahydrofuran (150 mL) dropwise over 10 min. The reaction mixture was stirred for 10 min and then piperylene (4 drops) was added. Most of the solvents were removed under a rapid stream of nitrogen, and the final traces were removed under vacuum (1 mm). The temperature of the flask was kept below 5 °C at all times. Tetrahydrofuran (200 mL) was added and the mixture stirred to dissolve the gum, the reaction mixture was then cooled to −60 °C, and the methyl cyanoformate (5.1 g, 60 mmol) in tetrahydrofuran (100 mL) was added. The reaction was stirred for 10 min and then quenched with saturated aqueous ammonium chloride solution (500 mL). The reaction mixture was extracted with ethyl acetate (2 × 100 mL). The combined extracts were washed with water (20 mL) and dried over sodium sulfate. This gave 20.84 g of an oil, which was purified by chromatography (80:20 cyclohexane/ethyl acetate). Two major fractions were isolated: **6**, 9.8 g, was crystallized from ether to give 6.12 g, 19 mmol, 33%: mp 97–100 °C NMR (360 MHz, $CDCl_3$) 1.35 (s, 3H), 1.46 (s, 3H), 1.86 (m, 1H, 10-β*H*), 2.07 (m, 1H, 4-α*H*), 2.5 (m, 1H, 4-β*H*), 2.6–2.95 (m, 6H), 3.72 (s, 3H, COO*Me*), 3.8 (s, 3H, 6-O*Me*), 6.71 (dd, *J* = 4, 11 Hz, 1H), 6.82 (d, *J* = 4 Hz, 1H), 6.99 (d, *J* = 11 Hz, 1H). The stereochemistry was confirmed by NOE experiments; MS (EI) 316 (M^+), 301, 284; IR ($CDCl_3$) 2950, 1735, 1705. Anal. $C_{19}H_{24}O_4$: C, H, N. A more polar fraction was found to be the acylated cyanohydrin **7**, as a gummy solid, 4.22 g, 10.52 mmol, 17.5%: NMR ($CDCl_3$) 128 (s, 3H), 1.40 (s, 3H), 1.2–2.9 (m, 9H), 3.78 (m, 3H), 3.83 (s, 6H), 6.70 (m, 2H), 6.97 (d, *J* = 10 Hz); MS (EI) 401 (M^+), 316, 258; IR ($CDCl_3$) 2950, 1760, 1730, 1605. Anal. $C_{22}H_{27}NO_6$: C, H, N. The desired keto–ester could be recovered from the cyanohydrin by treatment with 50% aqueous 1 M sodium hydroxide/tetrahydrofuran (100 mL) for 40 min. After extraction and crystallization of the product from ether, an additional 1.6 g, 5.06 mmol, 8.4%, of **6** was obtained.

8–11. The keto–ester **6** (316 mg, 1 mmol) was treated using the method described for **13** to give after chromatography (95:5 chloroform/methanol) four fractions.

1β,4aβ-Dimethyl-1α-(hydroxymethyl)-6-methoxy-1,2,3,4,4a,9,10,10a-octahydro-2β-phenantrenol (10) (43 mg, 0.148 mmol, 14.8%): mp 150–151 °C NMR ($CDCl_3$) 0.83 (s, 3H), 1.24 (s, 3H), 1.6–2.3 (m, 7H), 2.88 (m, 2H), 3.60 (m, 2H), 3.76 (s, 3H), 6.66 (dd, *J* = 10, 3 Hz, 1H), 6.82 (d, *J* = 3 Hz, 1H), 6.96 (d, *J* = 10 Hz, 1H); MS (EI) 290 (M^+), 272, 257. Anal. $C_{18}H_{26}O_3$: C, H, N.

1β,4aβ-Dimethyl-1α-(hydroxymethyl)-6-methoxy-1,2,3,4,4a,9,10,10a-octahydro-2α-phenanthrenol (8) (50 mg, 0.172 mmol, 17.2%): mp 159–161 °C; NMR (DMSO-d_6) 0.64 (s, 3H), 1.12 (s, 3H), 1.2–1.4 (m, 1H), 1.5–1.8 (m, 5H), 2.20 (m, 1H), 2.70 (m, 2H), 3.15 (dd, *J* = 12, 6 Hz, 1H), 3.5 (m, 2H), 4.67 (s, 3H), 4.38 (d, *J* = 5 Hz, 1H), 4.44 (t, *J* = 6 Hz, 1H), 6.63 (dd, *J* = 10, 2 Hz, 1H), 6.65 (d, *J* = 2 Hz, 1H), 6.90 (d, *J* = 10 Hz, 1H); MS (EI) 290 (M^+), 272, 257. Anal. $C_{18}H_{26}O_3$: C, H, N.

1β,4aβ-Dimethyl-1α-(hydroxymethyl)-1,2,3,4,4a,9,10,10a-octahydro-2α,6-phenanthrenediol (9) (57 mg, 0.197 mmol, 19.7%): mp 218 °C; NMR (DMSO-d_6) 0.75 (s, 3H), 1.12 (s, 3H), 1.6 (m, 3H), 1.9 (m, 3H), 2.7 (m, 2H), 3.20 (dd, *J* = 15, 4 Hz, 1H), 3.41 (dd, *J* = 15, 4 Hz, 1H), 3.56 (narrow m, 1H, *C2βH*), 4.33 (t, *J* = 4 Hz, 1H), 4.61 (d, *J* = 2.5 Hz, 1H), 6.46 (dd, *J* = 10, 2 Hz, 1H), 6.64 (d, *J* = 2 Hz, 1H), 6.77 (d, *J* = 10 Hz, 1H), 8.86 (s, 1H); MS (EI) 276 (M^+), 258, 243. Anal. $C_{17}H_{24}O_3$: C, H, N.

1β,4aβ-Dimethyl-1α-(hydroxymethyl)-1,2,3,4,4a,9,10,10a-octahydro-2β,6-phenanthrenediol (11) (64 mg, 0.235 mmol, 23.5%): mp >220 °C dec; NMR (DMSO-d_6) 0.63 (s, 3H), 1.10 (s, 3H), 1.3 (m, 1H), 1.6 (m, 5H), 2.1 (m, 1H), 2.68 (m, 2H), 3.15 (dd, *J* = 12.5, 5 Hz, 1H), 3.40 (dd, *J* = 12.5, 5 Hz, 1H), 3.52 (broad m, 1H, C2α*H*), 4.24 (d, *J* = 5 Hz, 1H), 4.42 (t, *J* = 5 Hz, 1H), 6.47 (dd, *J* = 10, 2 Hz, 1H), 6.60 (d, *J* = 2 Hz, 1H), 6.77 (d, *J* = 10 Hz, 1H), 8.85 (s, 1H); MS (EI) 276 (M^+), 258, 243. Anal. $C_{17}H_{24}O_3$: C, H, N.

1,4a-Dimethyl-7-formyl-6-methoxy-1,4,4a,9,10,10a-hexahydro-2-oxophenanthrene-1-carboxylic Acid, Methyl Ester (12). To the keto–ester **6** (50 mg, 0.16 mmol) in dry dichloromethane (5 mL) at 0 °C was added a 1 M solution of titanium tetrachloride in dichloromethane (1 mL, 1 mmol), followed by a solution of dichloromethyl methyl ether (20 mg, 0.17 mmol) in dichloromethane (1 mL). The reaction mixture was allowed to warm to room temperature for 20 min and then poured onto water and extracted with ether (2 × 20 mL). The extracts were washed with water (10 mL) and dried over sodium sulfate to give **12**: yield 50 mg, 0.145 mmol, 91%, sufficiently pure for most purposes. An analytical sample was prepared by chromatography (66:34 cyclohexane/ethyl acetate): mp 53–57 °C; NMR ($CDCl_3$) 1.36 (s, 3H), 1.46 (s, 4H), 1.5–1.22 (m, 3H), 2.45–2.6 (m, 1H), 2.68–3.0 (m, 5H), 3.72 (s, 3H), 3.89 (s, 3H), 6.85 (s, 1H), 7.52 (s, 1H), 10.48 (s, 1H); MS (EI) 344 (M^+), 329, 312. Anal. $C_{20}H_{24}O_5$: C, H, N.

1α,7-Bis(hydroxymethyl)-1β,4aβ-dimethyl-1,2,3,4,4a,9,10,10a-octahydro-2α,6-phenanthrenediol (14) and 1α,7-Bis(hydroxymethyl)-1β,4aβ-dimethyl-1,2,3,4,4a,9,10,10a-octahydro-2β,6-phenanthrenediol (13). To the aldehyde **12** (344 mg, 1 mmol) in toluene (10 mL) at −60 °C was added a 1 M solution of diisobutylaluminum hydride in toluene (10 mL, 10 mmol). The reaction mixture was allowed to warm to room temperature over 1 h and then refluxed for 2 h. The cooled reaction was poured onto saturated brine, acidified to pH 1 with dilute hydrochloric acid, and extracted with ethyl acetate. The extract was dried over sodium sulfate to give 180 mg of a solid which was purified by flash chromatography (95:5 chloroform/methanol) to give two products. **13**: 23 mg, 0.075 mmol, 7.5%; mp 97–105 °C; white solid; NMR (DMSO-d_6) 0.76 (s, 3H), 1.11 (s, 3H), 1.5–2.0 (m, 6H), 2.72 (m, 2H), 3.27 (d, *J* = 12.5 Hz, 1H), 3.43 (d, *J* = 12.5 Hz, 1H), 3.54 (broad s, 1H), 3.57 (m, 1H), 4.16 (broad s, 1H), 4.35 (broad s, 1H), 4.42 (s, 2H), 4.48 (broad s, 1H), 6.66 (s, 1H), 6.86 (s, 1H), 8.77 (s, 1H); MS (EI) 306 (M^+), 290, 288. Anal. $C_{18}H_{26}O_4$: C, H, N. HRMS for $C_{18}H_{26}O_4$. **14**: 21 mg, 0.075 mmol, 7.5%; mp 175–178 °C; white solid; NMR (DMSO-d_6) 0.62 (s, 3H), 1.08 (s, 3H), 1.2–1.42 (m, 1H), 1.5–1.8 (m, 5H), 2.07 (m, 1H), 2.7 (m, 2H), 3.20 (d, *J* = 11 Hz, 1H), 3.4–3.6 (m, 2H), 3.92 (broad s, 1H), 4.17 (broad s, 1H), 4.41 (s, 2H), 4.48 (broad s, 1H), 6.62 (s, 1H), 6.86 (s, 1H), 8.45 (broad s, 1H); MS (EI) 306 (M^+), 290, 288. Anal. $C_{18}H_{26}O_4 \cdot 0.8H_2O$: C, H, N. HRMS for $C_{18}H_{26}O_4$.

2,2,4aβ,10bβ-Tetramethyl-4a,4b,5,6,6a,7,8,9,10b,11,12,12a-dodecahydro-2*H*,4*H*-phenanthro[2,1-*d*][1,3]dioxan-9-one (15). **15** was prepared by the method of Bettolo[18b] from tetramethylperhydronaphtho[2,1-*d*][1,3]dioxan-7-one.[18c]

9-Oxo-2,2,4a,10b-tetramethyl-4a,4b,5,6,6a,7,8,9,10b,11,12,12a-dodecahydro-2*H*,4*H*-phenanthro[2,1-*d*][1,3]dioxane-8-carboxylate, Methyl Ester (16). To diisopropylamine (0.8 mL, 5.71 mmol) in tetrahydrofuran (10 mL) at −30 °C was added *n*-butyllithium (3.57 mL, 5.71 mmol, of a 1.6 M solution in cyclohexane), and the reaction mixture was stirred at 0 °C for 15 min. The reaction mixture was cooled to −60 °C, and **15** (1.65

g, 5.19 mmol) was added in tetrahydrofuran (10 mL). The reaction mixture was stirred at 0 °C for 1 h and then recooled to −60 °C, and methyl cyanoformate[14] (442 mg, 5.2 mmol) was added. The reaction mixture was allowed to warm to room temperature over 1 h, then poured into saturated aqueous ammonium chloride solution (75 mL), extracted with ethyl acetate (2 × 50 mL), and dried over sodium sulfate. Chromatography (75:25 cyclohexane/ethyl acetate) gave **16** (1.0 g, 2.66 mmol, 51%) as a mixture of isomers: NMR ($CDCl_3$) 0.80 (s, 3H), 1.17 (s, 3H), 1.87(s, 3H), 1.42 (s, 3H), 1.2–2.3 (m, 10 H), 2.4–2.83 (m, 2H), 3.31 (m, 2H), 3.62 (m, 2H), 3.70 and 3.76 (2 s, 3H, COO*Me*), 5.94 (narrow m, 1H); MS (EI) 376 (M^+), 361, 345. Anal. $C_{22}H_{32}O_5$: C, H, N.

1α,7α-Bis(hydroxymethyl)-1β,4aβ-dimethyl-1,2,3,4,4a,6,7,8,-8a,9,10,10a-dodecahydro-2α,6α-phenanthrenediol (17) and 1α,7α-Bis(hydroxymethyl)-1β,4aβ-dimethyl-1,2,3,4,4a,6,7,8,-8a,9,10,10a-dodecahydro-2α,6β-phenanthrenediol (18). To **16** (200 mg, 0.63 mmol) in toluene at −60 °C was added a 1 M toluene solution of diisobutylaluminum hydride (3.15 mL, 3.15 mmol). The reaction mixture was allowed to warm to 10 °C, and methanol (0.5 mL) was added. The volatiles were removed on a rotary evaporator and water (10 mL) and tetrahydrofuran (10 mL) added. The reaction mixture was acidified to pH 2 with dilute hydrochloric acid and stirred for 2 h when most of the acetonide had been hydrolyzed. Salt was added to saturate the water layer, and the mixture was extracted with chloroform (4 × 10 mL). The extracts were washed with saturated sodium bicarbonate solution (5 mL) and dried over sodium sulfate. Chromatography gave **18** (17 mg, 0.055 mmol, 8.7%): mp 93–95 °C; NMR ($CDCl_3$) 0.73 (s, 3H), 1.09 (s, 3H), 0.8–2.1 (m, 12 H), 2.36 (m, 1H), 3.40 (d, J = 10 Hz, 1H), 3.49 (d, J = 10 Hz, 1H), 3.71 (m, 3H), 4.18 (m, 1H, 12α*H*), 5.30 (narrow m, 1H); COSY and NOE experiments indicated the stereochemistry shown; MS (FAB) 333 (M + Na), 309. Anal. $C_{18}H_{30}O_4 \cdot 0.34H_2O$: C, H, N. Also isolated was **17** (6.0 mg, 0.019 mmol, 3.1%), contaminated by 10% of **18** above: mp 74–76 °C; NMR ($CDCl_3$) 0.73 (s, 3H), 1.10 (s, 3H), 1.15–2.1 (m, 11H), 2.3 (m, 1H), 3.93 (d, J = 11 Hz, 1H), 3.49 (d, J = 11 Hz, 1H), 3.73 (m, 2H), 4.41 (narrow m, 1H, C6β*H*), 5.47 (apparent d, J = 5 Hz, 1H, C5-*H*); COSY and NOE experiments indicated the stereochemistry shown; MS (FAB) 333 (M + Na), 309.

1β,4aβ-Dimethyl-6-methoxy-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-1-carboxylic Acid, Methyl Ester (19). The ester **19** was prepared from the keto–ester **6** (3.16 g, 10 mmol) according to the method of Hutchins:[33] yield 1.46 g, 4.83 mmol, 48%, after chromatography (95:5 cyclohexane/ethyl acetate); mp 73–76 °C; NMR ($CDCl_3$) 1.22 (s, 3H), 1.28 (s, 3H), 1.3–1.9 (m, 7H), 2.23 (m, 2H), 2.86 (m, 2H), 3.67 (s, 3H), 3.77 (s, 3H), 6.66 (dd, J = 2.5, 10 Hz, 1H), 6.80 (d, J = 2.5 Hz, 1H), 6.96 (d, J = 10 Hz); MS (EI) 302 (M^+), 287. Anal. $C_{19}H_{26}O_3$: C, H, N.

1β,4aβ-Dimethyl-7-formyl-6-methoxy-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-1-carboxylic Acid, Methyl Ester (20). **19** (906 mg, 1 mmol) was treated using the method described for **12** above to give **20** as a cream-colored solid: 963 mg, 2.92 mmol, 97%; mp 96–99 °C; NMR ($CDCl_3$) 1.24 (s, 3H), 1.29 (s, 3H), 1.35–1.9 (m, 7H), 2.21 (dd, J = 12.5, 2 Hz, 1H), 2.31 (m, 1H), 2.86 (m, 2H), 3.67 (s, 3H), 3.90 (s, 3H), 6.83 (s, 1H), 7.51 (s, 1H), 10.36 (s, 1H); MS (EI) 330 (M^+), 315, 255. Anal. $C_{20}H_{26}O_4$: C, H, N.

1β,4aβ-Dimethyl-7-formyl-6-hydroxy-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-1-carboxylic Acid (21). To **20** (55 mg, 0.167 mmol) was added a 1 M solution of sodium ethiolate in dimethylformamide (1.7 mL, 1.7 mmol), and the reaction mixture was heated to 120 °C for 3 h. The reaction mixture was cooled, poured onto water (20 mL), and extracted with ethyl acetate (2 × 20 mL). The extracts were dried over sodium sulfate. Chromatography (50:50 cyclohexane/ethyl acetate) gave **21** (7.2 mg, 0.0238 mmol, 14%): mp 222–225 °C; NMR ($CDCl_3$) 1.23 (s, 3H), 1.32 (s, 3H), 1.4–1.9 (m, 7H), 2.24 (m, 2H), 2.88 (m, 2H), 6.87 (s, 1H), 7.21 (s, 1H), 9.78 (s, 1H), 10.61 (broad s, 1H); MS (EI) 302 (M^+), 287, 256, 241. Anal. $C_{18}H_{22}O_4$: C, H, N.

1α,7-Bis(hydroxymethyl)-1β,4aβ-dimethyl-6-methoxy-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (22). To **20** (220 mg, 0.66 mmol) was added a 1 M solution of lithium borohydride in tetrahydrofuran (1.33 mL, 1.33 mmol), and the reaction mixture was stirred for 4 days. The reaction mixture was poured onto ice/dilute hydrochloric acid (50 mL) and extracted with ethyl acetate (2 × 20 mL). The extract was washed with water (10 mL) and dried over sodium sulfate. This gave a solid (210 mg), which was chromatographed (50:50 ethyl acetate/cyclohexane) to give **22** (100 mg, 0.33 mmol, 50%): mp 167–168 °C; NMR (DMSO-d_6) 0.76 (s, 3H), 1.14 (s, 3H), 1.22 (m, 2H), 1.4–1.8 (m, 6H), 2.29 (m, 1H), 2.68 (m, 2H), 2.93 (apparent dd, J = 10, 4 Hz, 1H), 3.22 (apparent dd, J = 17, 4 Hz, 1H), 3.72 (s, 3H), 4.40 (d, J = 4 Hz, 2H), 4.46 (t, J = 4 Hz, 1H), 4.76 (t, J = 4 Hz, 1H), 6.73 (s, 1H), 6.95 (s, 1H); MS (EI) 304 (M^+), 289, 287, 271. Anal. $C_{19}H_{28}O_3$: C, H, N.

1α,7-Bis(hydroxymethyl)-1β,4aβ-dimethyl-6-hydroxy-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (23). **20** (110 mg, 0.33 mmol) was treated using the method described for **13** above to give **23** (54 mg, 0.186 mmol, 56.4%) after chromatography (50:50 cyclohexane/ethyl acetate). Crystallization from ethyl acetate/cyclohexane gave an analytical sample: 23 mg; mp 195–196 °C; NMR (DMSO-d_6) 0.76 (s, 3H), 1.10 (s, 3H), 1.20 (m, 2H), 1.4–1.8 (m, 6H), 2.1 (m, 1H), 2.67 (m, 2H), 2.91 (dd, J = 11, 5 Hz, 1H), 3.4 (obscured m, 1H), 4.38 (d, J = 4 Hz, 2H), 4.42 (t, J = 4 Hz, 1H), 4.72 (t, J = 5 Hz, 1H), 6.62 (s, 1H), 6.86 (s, 1H), 8.77 (s, 1H); MS (EI) 290 (M^+), 272, 259. Anal. $C_{18}H_{26}O_3$: C, H, N.

1β,4aβ-Dimethyl-7-(hydroxymethyl)-6-methoxy-1,2,3,4,-4a,9,10,10a-octahydrophenanthrene-1-carboxylic Acid, Methyl Ester (24). To **20** (110 mg, 0.33 mmol) in tetrahydrofuran (10 mL) at 0 °C was added a 1 M solution of lithium borohydride in tetrahydrofuran (0.35 mL, 0.35 mmol). The reaction mixture was stirred at 0 °C for 1 h, poured onto ice/dilute hydrochloric acid (50 mL), and extracted with ethyl acetate (2 × 10 mL). The extract was dried over sodium sulfate to give **24** in quantitative yield as a gum: NMR (DMSO-d_6) 1.17 (s, 3H), 1.22 (s, 3H), 1.3 (m, 2H), 1.67 (m, 5H), 2.2 (d, J = 12 Hz, 1H), 2.86 (m, 1H), 2.72 (m, 2H), 3.62 (s, 3H), 3.72 (s, 3H), 4.49 (d, J = 6 Hz, 2H), 4.77 (t, J = 6 Hz, 1H), 6.74 (s, 1H), 6.97 (s, 1H); MS (EI) 332 (M^+), 316, 299, 257; HRMS for $C_{20}H_{28}O_4$.

1β,4aβ-Dimethyl-6-hydroxy-7-(hydroxymethyl)-1,2,3,4,-4a,9,10,10a-octahydrophenanthrene-1-carboxylic Acid (25). **24** (65 mg, 0.196 mmol) was treated using the method described for **26** but using 5 equiv of sodium *p*-thiocresolate (142 mg, 1 mmol) and refluxing for 4 h. Chromatography (1:2.5:96.5 acetic acid/methanol/chloroform) gave **25** (8.6 mg, 0.028 mmol, 14.4%): mp 230 °C dec; NMR (DMSO-d_6) 1.1 (s, 3H), 1.13 (s, 3H), 1.2–1.8 (m, 7H), 2.11 (m, 2H), 2.66 (m, 2H), 4.40 (s, 2H), 6.62 (s, 1H), 6.86 (s, 1H); MS (EI) 304 (M^+), 286, 271, HRMS for $C_{18}H_{24}O_4$.

1β,4aβ-Dimethyl-7-(hydroxymethyl)-6-methoxy-1,2,3,4,-4a,9,10,10a-octahydrophenanthrene-1-carboxylic acid (26). To **24** (110 mg, 0.33 mmol) in dimethylformamide (2 mL) was added sodium *p*-thiocresolate[34] (51 mg, 0.35 mmol), and the reaction mixture was refluxed for 2 h. The reaction mixture was cooled, poured onto ice/dilute hydrochloric acid (20 mL), and extracted with ethyl acetate (2 × 10 mL). The extract was washed with water and dried over sodium sulfate. Chromatography (1: 2.5:96.5 acetic acid/methanol/chloroform) gave **26** (16 mg, 0.05 mmol, 15%): mp 176–181 °C; NMR ($CDCl_3$) 1.22 (s, 3H), 1.28 (s, 3H), 1.52 (m, 2H), 1.76 (m, 5H), 2.23 (m, 2H), 2.83 (m, 2H), 3.83 (s, 3H), 4.61 (s, 2H), 6.73 (s, 1H), 6.91 (s, 1H); MS (EI) 318 (M^+), 304, 285, 227; HRMS for $C_{19}H_{26}O_4$.

1β,4aβ-Dimethyl-6-methoxy-1,2,4,4a,9,10,10a-octahydrophenanthrene-1-carboxylic Acid (27). **19** (735 mg, 2.43 mmol) was treated using the method described for **26** but using 1.5 equiv of sodium thiocresolate (532 mg, 3.65 mmol) and heating to 120 °C for 3 h. Chromatography (80:20 cyclohexane/ethyl acetate) gave **27** (296 mg, 1.03 mmol, 38%): mp 142–145 °C; NMR ($CDCl_3$) 1.22 (s, 3H), 1.38 (s, 3H), 1.52 (m, 2H), 1.74 (m, 5H), 2.25 (m, 2H), 2.84 (m, 2H), 3.77 (s, 3H), 6.66 (dd, J = 7.5, 1.5 Hz, 1H), 6.78 (d, J = 1.5 Hz, 1H), 6.96 (d, J = 7.5 Hz). MS (EI) 288 (M^+), 273, 227. Anal. $C_{18}H_{24}O_3$: C, H, N.

1β,4aβ-Dimethyl-6-methoxy-1,2,3,4,4a,9,10,10a-octahydro-1-phenanthrenamine (28). To **27** (176 mg, 0.61 mmol) in *tert*-butyl alcohol (5 mL) was added triethylamine (68 mg, 92 μL, 0.67 mmol) and diphenyl phosphoroazidate[19] (185 mg, 144 μL, 0.67 mmol). The reaction mixture was refluxed for 1 h, and then the *tert*-butyl alcohol was removed on a rotary evaporator. The residue was dissolved in tetrahydrofuran (10 mL) and dilute hydrochloric acid (5 mL) added. The reaction mixture was stirred

overnight, adjusted to pH 12 with sodium hydroxide solution, and extracted with ethyl acetate (3 × 10 mL). The extract was washed with water and dried over sodium sulfate. Chromatography (1:5:94 triethylamine/methanol/chloroform) gave **28** (77 mg, 0.3 mmol, 49%): NMR ($CDCl_3$) 1.10 (s, 3H), 1.17 (s, 3H), 1.2–1.8 (m, 7H), 2.05 (m, 1H), 2.21 (m, 1H), 2.85 (m, 2H), 3.76 (s, 3H), 6.66 (dd, J = 9, 2 Hz, 1H), 6.80 (d, J = 2 Hz, 1H), 6.95 (d, J = 9 Hz, 1H); MS (EI) 259 (M^+), 242, 227; HRMS for $C_{17}H_{25}NO$.

Chiral Compounds. 7-Methoxy-1-methyl-2-tetralone (29). To methylmagnesium iodide (0.741 mol) in ether (500 mL) was added toluene (100 mL) followed by 7-methoxy-1-tetralone (100 g, 0.57 mol) at such a rate as to maintain a steady reflux. The reaction mixture was refluxed for 2 h and cooled, and saturated aqueous ammonium chloride (500 mL) was added slowly. The upper layer was separated, washed with water, and dried over sodium sulfate. The ether was removed on a rotary evaporator and then *p*-toluene sulfonic acid (500 mg) added, and the solution was refluxed in a Dean–Stark water separator for 30 min. The cooled reaction mixture was washed with saturated sodium bicarbonate solution (50 mL) and dried over sodium sulfate to give 1-methyl-7-methoxy-3,4-dihydronaphthalene (95.87 g, 0.55 mol, 96.7%) sufficiently pure for the next stage. The above product (17.4 g, 0.1 mol) in acetone (40 mL) was added to a solution of *N*-methylmorpholine *N*-oxide (12.9 g, 0.11 mol), osmium tetroxide[18] (100 mg, 0.4 mmol) in acetone (40 mL), *tert*-butyl alcohol (40 mL), and water (60 mL). The reaction mixture was stirred at 50 °C for 1.5 h. The volatiles were removed on a rotary evaporator, and water (200 mL) was added. The aqueous mixture was extracted with ethyl acetate (2 × 100 mL), and the extracts were washed with 1% aqueous sodium metabisulfite (50 mL), and saturated aqueous sodium bicarbonate (50 mL) and dried over sodium sulfate. The solvent was removed, the intermediate diol was taken up in toluene (200 mL), and *p*-toluenesulfonic acid (700 mg) was added. The reaction mixture was refluxed for 15 min in a Dean–Stark water separator, cooled, washed with saturated aqueous sodium bicarbonate, and dried over sodium sulfate. Removal of solvent and crystallization from ether (80 mL) at −70 °C gave **29** (11.56 g, 0.061 mol, 61%) as an unstable hygroscopic solid. The solid could be stored for several weeks in the freezer: mp 38–40 °C; NMR ($CDCl_3$) 1.46 (d, J = 7.5 Hz, 3H), 2.53 (m, 2H), 3.0 (m, 2H), 3.48 (q, J = 7.5 Hz, 1H), 3.82 (s, 3H), 6.77 (m, 2H), 7.13 (d, J = 8 Hz, 1H); MS (EI) 190 (M^+), 148. $C_{12},H_{14},O_2 \cdot 0.1H_2O$: C, H, N.

(4a*S*)-1,4a-Dimethyl-6-methoxy-4,4a,9,10-tetrahydro-2-(3*H*)-phenanthrenone (30). The tetralone **29** (19.0 g, 0.1 mol), (*R*)-(+)-α-methylbenzylamine (13.31 g, 0.11 mol) and *p*-toluenesulfonic acid (150 mg) were refluxed under Dean–Stark conditions for 4 h. The toluene was removed on a rotary evaporator and tetrahydrofuran (200 mL) added followed by ethyl vinyl ketone (11.78 g, 14 mL, 0.14 mol). The reaction mixture was stirred overnight, 20% aqueous acetic acid (200 mL) was added, and the reaction mixture was stirred for 1 h. The volatiles were removed on the rotary evaporator. The residue was taken up in ethyl acetate (200 mL), washed with saturated aqueous sodium bicarbonate, and dried over sodium sulfate to give crude ketol (27.65 g, 0.097 mol). The ketol was treated with sodium methoxide solution (2.24 g, 0.097 mol) in 200 mL of methanol and refluxed for 2 h. The methanol was removed on the rotary evaporator. The residue was taken up in ethyl acetate (200 mL), washed with water, and dried over sodium sulfate. Chromatography (85:15 cyclohexane/ethyl acetate) gave crude product which was crystallized from ether (45 mL) and hexane (45 mL) at −10 °C to give **30** as large pale yellow crystals (5.4 g, 21.1 mmol, 21%): mp 69–71 °C; $[\alpha]^{589}_D$ = +293.1; NMR ($CDCl_3$) 1.52 (s, 3H), 1.85 (s, 3H), 2.06 (m, 1H), 2.3–3.1 (m, 7H), 3.80 (s, 3H), 6.72 (dd, J = 9, 2 Hz, 1H), 6.84 (d, J = 2 Hz, 1H), 7.03 (d, J = 9 Hz, 1H); this sample was shown to be >96% ee by NMR studies with the chiral shift reagent Eu(thc)$_3$; MS (EI) 256 (M^+), 241, 225. Anal. $C_{17}H_{20}O_2$: C, H, N. A small sample was recrystallized from ethanol: mp 70–71 °C; $[\alpha]^{589}_D$ = +324.1, CD Δε at 234.3 nm, +14.5. This sample had the X-ray structure shown in Figure 2.

(4a*R*)-1,4a-Dimethyl-6-methoxy-4,4a,9,10-tetrahydro-2-(3*H*)-phenanthrenone (31) was prepared exactly as for the 10-(*S*) isomer but using *S* -(−)-α-methylbenzylamine as chiral auxilliary. **31**: $[\alpha]^{589}_D$ = −320.3; CD Δε at 234.3 nm, −14.8.

(1*S*,4a*S*,10a*R*)-1,4a-Dimethyl-6-methoxy-1,4,4a,9,10,10a-hexahydro-2-oxophenanthrene-1-carboxylic acid, methyl ester (32) was prepared exactly as for the racemic ester **6** but using **30** as starting material. **32**, a clear oil, had the following additional data: CD Δε at 220 nm, +3.4, at 290 nm, Δε −0.66.

(1*R*,4a*R*,10a*S*)-1,4a-Dimethyl-6-methoxy-1,4,4a,9,10,10a-hexahydro-2-oxophenanthrene-1-carboxylic acid, methyl ester (33) was prepared exactly as for the racemic ester but using **31** as a starting material. **33**, a clear oil, had the following additional data: CD Δε at 220 nm, −2.97, at 290 nm, Δε 1.07.

(1*S*,4a*S*,10a*R*)-1,4a-Dimethyl-7-formyl-6-methoxy-1,4,4a,9,-10,10a-hexahydro-2-oxophenanthrene-1-carboxylic Acid, Methyl Ester (34) and (1*R*,4a*R*,10a*S*)-1,4a-Dimethyl-7-formyl-6-methoxy-1,4,4a,9,10,10a-hexahydro-2-oxophenanthren-1-carboxylic Acid, Methyl Ester (35). The aldehydes were prepared exactly as for the racemic aldehyde **12** above and used crude for the preparation of **36–39** below.

36 and 37. Using **34** as starting material and the method described for the racemic tetrol **13** above, **(+)-(1*S*,2*R*,4a*S*,10a*R*)-1,7-bis(hydroxymethyl)-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydro-2,6-phenanthrenediol (36) and (+)-(1*S*,2*S*,4a*S*,-10a*R*)-1,7-bis(hydroxymethyl)-1,4a-dimethyl-1,2,3,4,4a,9,10,-10a-octahydro-2,6-phenanthrenediol (37)** were prepared which had the following additional data. **36**: mp 200 °C dec; CD 230 nm, Δε = +2.45. Anal. $C_{18}H_{26}O_4 \cdot 0.26MeOH$: C, H, N. **37**: mp 109–112 °C; CD at 230 nm Δε = +2.54 $C_{18}H_{26}O_4 \cdot 0.42MeOH$: C, H, N.

38 and 39. Using **35** as starting material and the method described for the racemic tetrol **13** above, **(−)-(1*R*,2*S*,4a*R*,10a*S*)-1,7-bis(hydroxymethyl)-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydro-2,6-phenanthrenediol (38)** and **(−)-(1*R*,2*R*,4a*R*,-10a*S*)-1,7-bis(hydroxymethyl)-1,4a-dimethyl-1,2,3,4,4a,9,10,-10a-octahydro-2,6-phenanthrenediol (39)** were prepared which had the following additional data. **38**: mp 249 °C dec; CD 230 nm, Δε = −2.47. Anal. $C_{18}H_{26}O_4$: C, H, N. **39**: mp 143–149 °C dec; CD Δε at 230 nm = −3.04. Anal. $C_{18}H_{26}O_4 \cdot 0.4MeOH$: C, H, N.

40 and 41. Prepared as for **13** above but using **34** as starting material and quenching the reaction on warming the reaction from −70 to 0 °C.

(1*S*,2*R*,4a*S*,10a*R*)-1,7-Bis(hydroxymethyl)-6-methoxy-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydro-2-phenanthrenol (40): mp 64–66 °C; NMR (DMSO-d_6) 0.77 (s, 3H), 1.16 (s, 3H), 1.1–2.05 (m, 7H), 2.73 (m, 2H), 3.23 (apparent dd, J = 20, 6 Hz, 1H), 3.44 (apparent dd, J = 12.5, 6 Hz, 1H), 3.57 (narrow m, 1H, C2α*H*), 3.71 (s, 3H), 4.35 (m, 1H), 4.40 (d, J = 5 Hz, 2H), 4.62 (d, J = 2.5 Hz, 1H), 4.74 (t, J = 5 Hz, 1H), 6.76 (s, 1H), 6.97 (s, 1H); MS (EI) 320 (M^+), 302, 287. Anal. $C_{18}H_{28}O_4 \cdot 0.16CHCl_3$; C, H, N. CD at 227.6 nm, Δε = +4.23.

(1*S*,2*S*,4a*S*,10a*R*)-1,7-Bis(hydroxymethyl)-6-methoxy-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydro-2-phenanthrenol (41): mp 169–172 °C; NMR (DMSO-d_6) 0.65 (s, 3H), 1.14 (s, 3H), 1.42 (m, 1H), 1.67 (m, 5H), 2.26 (m, 1H), 2.73 (m, 2H), 3.17 (m, 1H), 3.40 (m, 1H), 3.52 (m, 1H, C2β*H*), 3.72 (s, 3H), 4.26 (d, J = 5 Hz, 1H), 4.40 (d, J = 5 Hz, 2H), 4.43 (t, J = 4 Hz, 1H), 4.76 (t, J = 5 Hz, 1H), 6.73 (s, 1H), 6.96 (s, 1H); MS (EI) 320 (M^+), 302, 287, 269. Anal. $C_{19}H_{28}O_4 \cdot 0.38CHCl_3$: C, H, N. CD at 227.6 nm, Δε = +4.46.

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