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Structural Parallels Between the Cardiotonic Steroids and the *Erythrophleum* Alkaloids - II. Synthesis and Na^+,K^+-ATPase Inhibitory Activity of Novel *Erythrophleum* Alkaloid Analogues

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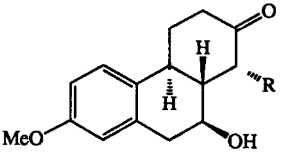
Abstract *Erythrophleum* alkaloid analogues, which differ in the ester side-chain configuration, in the nature of the 14-axial substituent (H, Me, Et) and in their absolute configuration, have been prepared A pronounced trend towards increased Na^+,K^+-ATPase inhibitory activity occurs through the H, Me and Et series, with the *E* side-chain configuration more active than the Z This trend is largely confined to the analogues with an absolute configuration matching that of the natural alkaloids A structural parallel between the 14-axial alkyl substituent of the alkaloids and the D-ring of the cardiotonic steroids is proposed

In Part 1[1] we reported the synthesis of the phenanthrenones (1), (2) and (3) and now describe their conversion to analogues of the *Erythrophleum* alkaloids possessing B- and C-ring functionality present in the natural products, but largely ignored in previous structure-activity studies

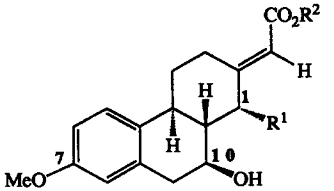


(1) R = H (2) R = Me (3) R = Et

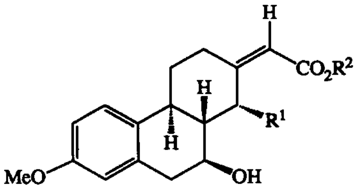
Introduction of the required α,β-unsaturated ester side-chain into the phenanthrenone (1) was accomplished by a Horner-Emmons[2] reaction with the lithium salt of triethylphosphonoacetate carbanion in tetrahydrofuran for two hours at room temperature The *E* and *Z* isomers (4) and (5) were formed in a ratio of *ca* 2 1 respectively, in a total yield of 76%, and could be separated by careful radial chromatography using 15% ethyl acetate/toluene as eluant, in other solvent systems the isomers were co-incident.

Treatment of the methyl-substituted phenanthrenone (2) under the same Horner-Emmons reaction conditions gave the *E*-α,β-unsaturated ester (6) in 43% yield, with only a trace of the *Z* isomer (7) evident by t l c analysis, the ethyl-substituted phenanthrenone (3) failed to react at all

Since for the purpose of comparison of biological activity we required the *E* and *Z* isomers in both the methyl- and ethyl-substituted series, an alternative olefination procedure was followed. The alcohol group of (**2**) was protected as its THP ether (using 2,6-dimethylpyridinium *p*-toluenesulphonate as catalyst to avoid epimerisation of the methyl group[1]) and the ketone was then treated with ethyl lithio(trimethylsilyl)acetate [3] Removal of the THP protecting group (pyridinium *p*-toluenesulphonate/ethanol), followed by radial chromatography, ga [illegible] *E* and *Z* isomers (**6**) and (**7**) in overall yields from (**2**) of 39% and 21% respectively In a precisely analog [illegible] nner the ethyl-phenanthrenone (**3**) was transformed, *via* the THP derivative, into the *E* and *Z* isomers (**8**) and (**9**) in 21% and 44% yield respectively The decreased preference for the *E* configuration in the Peterson olefination with ethyl lithio(trimethylsilyl)acetate was anticipated on the basis of work by Battiste *et al* [4] who found that the stereoselectivity of the Peterson olefination is often complementary to that of the Horner-Emmons reaction



(**4**) $R^1 = H$, $R^2 = Et$
(**6**) $R^1 = Me$, $R^2 = Et$
(**8**) $R^1 = Et$, $R^2 = Et$
(**10**) $R^1 = H$, $R^2 = CH_2CH_2NMe_2$
(**12**) $R^1 = Me$, $R^2 = CH_2CH_2NMe_2$
(**14**) $R^1 = Et$, $R^2 = CH_2CH_2NMe_2$



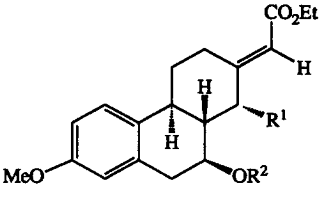
(**5**) $R^1 = H$, $R^2 = Et$
(**7**) $R^1 = Me$, $R^2 = Et$
(**9**) $R^1 = Et$, $R^2 = Et$
(**11**) $R^1 = H$, $R^2 = CH_2CH_2NMe_2$
(**13**) $R^1 = Me$, $R^2 = CH_2CH_2NMe_2$
(**15**) $R^1 = Et$, $R^2 = CH_2CH_2NMe_2$

Assignment of the *E* and *Z* configuration to compounds (**4**) to (**9**) followed from analysis of the ^{1}H n m r and ^{13}C n m r spectra of the isomers In the ^{1}H n m r spectra of the isomers deshielding of the equatorial hydrogen at either C-1 or C-3 by the proximate side-chain carbonyl group of the *Z* and *E* isomers respectively allowed the isomers to be readily differentiated [5] The shielding of C-1 or C-3 in the ^{13}C n m r spectra of the isomers due to the γ-effect[6] of the side-chain carbonyl group confirmed the stereochemical assignments

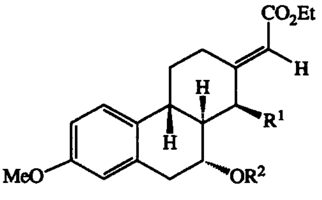
All of the alkyl-substituted products (**6**), (**7**), (**8**) and (**9**) retained the alkyl group in the axial configuration This was concluded from the magnitude of the coupling constant between H-1 and H-10a in the ^{1}H n m r spectra of the respective compounds (4 Hz in each case) Comparison of the ^{13}C n m r spectra of (**6**) and (**7**) with those of the corresponding des-methyl compounds (**4**) and (**5**) revealed a shielding effect at C-3 (4 5 p p m for (**6**) and 3 0 p p m for (**7**)), C-4a (6 8 and 7 0 p p m) and C-10 (3 7 and 3 8 p p m), also indicating that the methyl group remained axial in (**6**) and (**7**)[7] Similar observations were made in the ^{13}C n m r spectra of the ethyl-substituted products (**8**) and (**9**)

The *α,β*-unsaturated ethyl esters (**4**) to (**9**) were converted to the 2-(dimethylamino)ethyl esters (**10**) to (**15**) by hydrolysis of the ethyl ester (aqueous sodium hydroxide in dioxane), and then re-esterification with 2-(dimethylamino)ethanol using 2-bromo-1-methylpyridinium iodide as the coupling agent [8] The overall yields of the alkaloid analogues thus obtained were in the range 69-97%

In order to unequivocally demonstrate the structural specificity of the interaction of our analogues with the enzyme Na^+,K^+-ATPase, it was decided to resolve key analogues into their constituent enantiomers [9] This has been efficiently carried out by separation of the diastereomers resulting from esterification of the B-ring hydroxyl groups of (**4**) and (**8**) with an enantiomerically pure chiral acid Esterification of (**4**) with (*R*)-(-)-*O*-methylmandelic acid, using oxalyl chloride/dimethylformamide as the coupling agent,[10] gave the mixture of diastereomers (**16**) and (**17**) The mixture was separable by careful radial chromatography on a small scale (*ca* 100 mg) but attempts to scale up the separation failed. Esterification of (**4**) with (1*S*)-(-)-camphanic acid gave the mixture of (**18**) and (**19**), but the diastereomers were again chromatographically inseparable on a preparative scale It was found, however, that a single fractional crystallisation of the mixture afforded one of the diastereomers in a highly crystalline form, in 36% yield from the racemic alcohol (**4**) H p l c analysis of the crystalline fraction indicated a 100% diastereomeric excess (d.e) of the shorter retention time diastereomer The configuration of this diastereomer (**18**) was determined by X-ray crystallography (Figure 1) and the absolute configuration of the parent alcohol was thus inferred to be (4a*S*,10*S*,10a*S*)

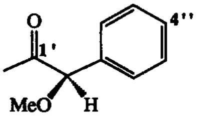


(**16**) R^1 = H, R^2 = A^1
(**18**) R^1 = H, R^2 = A^2
(**20**) R^1 = Et, R^2 = A^1

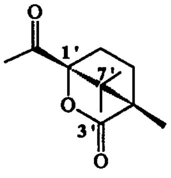


(**17**) R^1 = H, R^2 = A^1
(**19**) R^1 = H, R^2 = A^2
(**21**) R^1 = Et, R^2 = A^1

A^1 =



A^2 =



H p l c analysis of the mother liquor from fractional crystallisation of (**18**) indicated an 86% d e of the longer retention time diastereomer (**19**) All attempts to induce crystallisation failed Consequently, the camphanate group of (**19**) was removed by transesterification with K_2CO_3 in ethanol, and the alcohol group was re-esterified with (*R*)-(-)-*O*-methylmandelic acid A single fractional crystallisation afforded the (4a*R*,10*R*,10a*R*)-*O*-methylmandelate (**17**), of 100% d e by h p l c analysis, in 24% overall yield from the racemate (**4**)

Optical resolution of the axial 1-ethyl compound (**8**) proceeded more smoothly than in the case of (**4**) Esterification of (**8**) with (*R*)-(-)-*O*-methylmandelic acid, again using oxalyl chloride/dimethylformamide as the coupling agent,[10] gave a mixture of diastereomers (**20**) and (**21**), which were readily separable by radial chromatography The two diastereomers were isolated in 47% and 46% yield respectively, and each was shown to be of 100% d e by h p l c analysis The longer retention time isomer (**21**) was crystalline, and its configuration was determined by X-ray crystallography (Figure 2), again allowing the absolute configuration of the parent alcohol to be inferred as (1*S*,4a*R*,10*R*,10a*R*)

Removal of the camphanate group from (**18**) and the *O*-methylmandelate groups from (**17**), (**20**) and (**21**) by transesterification with K_2CO_3/ethanol, afforded the optically active alcohols (+)-(**4**), (-)-(**4**), (+)-(**8**) and (-)-(**8**) in yields of 71%, 92%, 87% and 80% respectively The optically active ethyl esters were then converted to the optically active alkaloid analogues (+)-(**10**), (-)-(**10**), (+)-(**14**) and (-)-(**14**) using the same procedure described for the preparation of the racemic analogues.

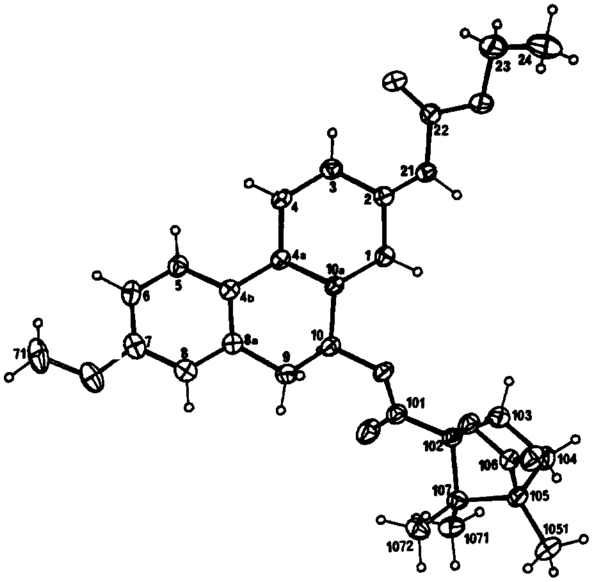


Figure 1 Projection of (**18**) perpendicular to the fused ring plane, 20% thermal ellipsoids are shown for the non-hydrogen atoms, with carbon numbering Hydrogen atoms have arbitrary radii of 0 1 Å

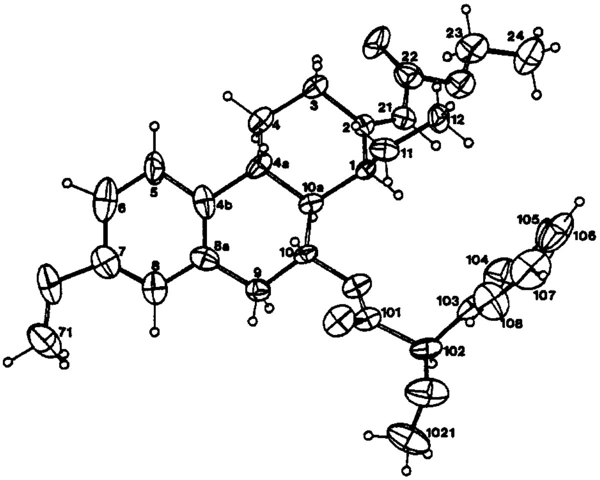
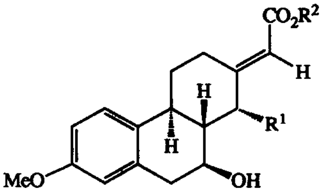
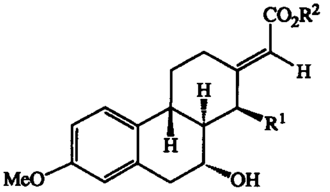


Figure 2 Projection of (**21**) perpendicular to the fused ring plane, 20% thermal ellipsoids are shown for the non-hydrogen atoms, with carbon numbering Hydrogen atoms have arbitrary radii of 0 1 Å



(+)-(**4**) $R^1 = H, R^2 = Et$
(+)-(**8**) $R^1 = Et, R^2 = Et$
(+)-(**10**) $R^1 = H, R^2 = CH_2CH_2NMe_2$
(+)-(**14**) $R^1 = Et, R^2 = CH_2CH_2NMe_2$



(-)-(**4**) $R^1 = H, R^2 = Et$
(-)-(**8**) $R^1 = Et, R^2 = Et$
(-)-(**10**) $R^1 = H, R^2 = CH_2CH_2NMe_2$
(-)-(**14**) $R^1 = Et, R^2 = CH_2CH_2NMe_2$

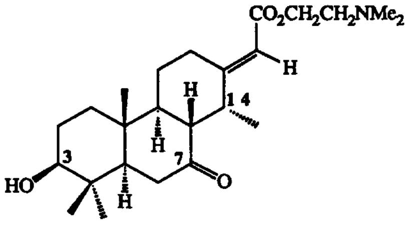
A preliminary assessment of the ability of our analogues to inhibit Na^+,K^+-ATPase isolated from porcine cerebral cortex is summarised in Table 1. Under the conditions of the assay the IC_{50} of the *Erythrophleum* alkaloid cassaine (**22**) was found to be 1 1 *μM*, which is comparable to the values reported for the inhibition by (**22**) of Na^+,K^+-ATPase isolated from human heart ventricle[11] (0 65 *μM*) and from calf[12] or dog hearts[13] (each 1 *μM*).

A comparison of the IC_{50} of compound (**10**) with those of the other racemic analogues with the *E* configuration, (**12**) and (**14**), revealed that a significant increase in Na^+,K^+-ATPase inhibitory activity occurs through introduction of the axial methyl group, and that a further increase takes place through introduction of the axial ethyl group The same trend, but with reduced magnitude, was observed with the less active *Z* isomers (**11**), (**13**) and (**15**)

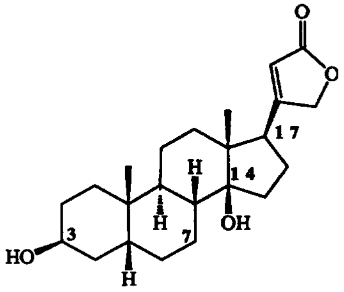
The most active of the analogues, the optically pure ethyl-substituted compound (+)-(**14**) had an inhibitory activity approaching that of the natural alkaloid cassaine (**22**) The absolute configuration of this compound matches that of the corresponding chiral centres in the B- and C-rings of cassaine (**22**) The enantiomeric analogue (-)-(**14**) was much less active For the optically pure analogues lacking alkyl substitution, (+)-(**10**) and (-)-(**10**), there was a less substantial difference in activity between the enantiomers, however, it is again the analogue with an absolute configuration matching that of cassaine (**22**) that is the more active The increase in activity observed on introduction of the axial ethyl group into the racemic analogues is seen to be largely confined to the analogues with an absolute configuration matching that of the natural alkaloids

Table 1. Na^+,K^+-ATPase inhibitory activities of the analogues prepared in this study

Compound	IC_{50} (*μM*)
(**10**)	500
(+)-(**10**)	200
(-)-(**10**)	1500
(**11**)	1400
(**12**)	25
(**13**)	200
(**14**)	8 7
(+)-(**14**)	3 8
(-)-(**14**)	930
(**15**)	50
cassaine (**22**)	1 1



(22)



(23)

Previous structure-activity studies on the cardiotonic steroids carried out by Fullerton *et al*[14] demonstrate that the position of the side-chain carbonyl oxygen atom of the steroids plays a critical role in determining both Na^+,K^+-ATPase inhibitory activity and inotropic activity, and suggest that the presence of a *cis*-fused D-ring does not play a significant *direct* role in determining activity. However, Repke *et al.*[15] have proposed that the presence of the *cis*-fused D-ring is important in determining the specificity of action of the cardiotonic steroids Steroid analogues lacking a *cis*-fused D-ring, although able to inhibit Na^+,K^+-ATPase, often do not elicit a positive inotropic effect [16-18] It has been suggested[15] that these analogues are also capable of inhibiting other intracellular metabolic processes (for example digitalis-insensitive mitochondrial Mg^{2+}-ATPase[19]) which interferes with the development of a positive inotropic effect. In view of the biochemical evidence indicating that the cardiotonic steroids and the *Erythrophleum* alkaloids share the same binding site on Na^+,K^+-ATPase,[13,20] we propose that the supposed sub-site for the D-ring of the cardiotonic steroids also accommodates the axial ethyl group of our analogues, and presumably the 14α-methyl group of the natural alkaloids

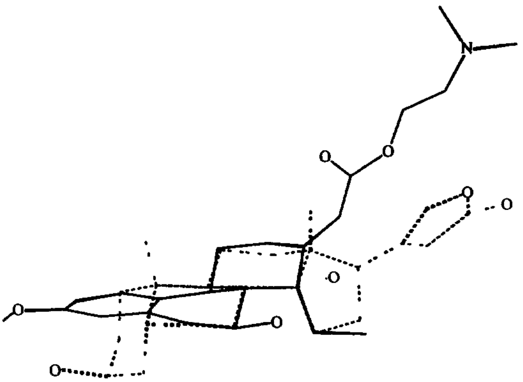


Figure 3 Superimposition of (+)-(**14**) with digitoxigenin (**23**)

We have modelled the structure of (+)-(**14**)[21] with the side-chain in an s-cis,syn conformation,[24] and superimposed it with the X-ray crystal structure of digitoxigenin (**23**)[25] (Figure 3) The predicted minimum energy conformation of the ethyl group in the modelled structure has a C10a-C1-C11-C12 (phenanthrene numbering, where C11 and C12 are the methylene and methyl carbons respectively of the ethyl group) torsion angle of -167°, close to that observed in the X-ray crystal structure of **(21)** (-178° for the enantiomer of **(21)**, Figure 2) The preference for this conformation of the ethyl group is supported by the ^{1}H n.m.r. spectral data of compounds **(8)**, **(9)**, **(14)** and **(15)** In each case the coupling constants to H-1 from the ethyl group methylene protons were 4 Hz and 11 5 Hz, suggesting the predominance of a conformation with a C10a-C1-C11-C12 torsion angle of around 180° or -60° [26] However, molecular modelling has indicated that the -60° conformation is significantly disfavoured through an unfavourable steric interaction between the terminal methyl and H-10 The superimposition, carried out by minimising the squared distances between C-5 through to C-16 of digitoxigenin **(23)** and the corresponding atoms of the B- and C-rings and axial ethyl group of the analogue, illustrates the proposed structural parallel between the axial ethyl group and the D-ring of digitoxigenin **(23)**

Crystallography

Structure determination Unique data sets were measured at ~ 295 K to the specified $2\theta_{max}$ limit using an ENRAF-Nonius CAD-4 diffractometer (monochromatic Mo $K\alpha$ radiation source (λ = 0 71073Å), $2\theta/\theta$ scan mode) N Independent reflections were obtained, N_o with $I > 3\sigma(I)$ being considered 'observed' and used without absorption correction in the full matrix least squares refinements after solution of the structures by direct methods Anisotropic thermal parameters were refined for C,O, $(x, y, z, U_{iso})_H$ were included, constrained at estimated values Conventional residuals R, R_w on $|F|$ are quoted at convergence, statistical weights derivative of $\sigma^2(I) = \sigma^2(I_{diff}) + n_w \times 10^{-4}\sigma^4(I_{diff})$ were employed Neutral atom complex scattering factors were employed, chirality being assigned on internal chemical grounds, computation used the XTAL 2.6 program system implemented by S R Hall Pertinent results are given in Figures 1 and 2, and Table 2, material deposited with the journal comprises thermal and hydrogen atom parameters, molecular non-hydrogen geometries and structure factor amplitudes

Crystal/refinement data

(18) $C_{29}H_{36}O_7$, M_r = 496 6 Orthorhombic, space group $P2_12_12_1$ (D_2^4, No 19), a = 17 623(2), b = 15 564(2), c = 9 723(1) Å, V = 2667 Å^3 D_c (Z = 4) = 1 24 g cm^{-3}, F(000) = 1064 μ_{Mo} = 0 5cm^{-1}, specimen 0 42 x 0 40 x 0 25 mm $2\theta_{max}$ = 50°, N = 2658, N_o = 1880, R = 0 045, R_w = 0 049 (n_w = 7)

(21) $C_{30}H_{36}O_6$, M_r = 492 6 Orthorhombic, space group $P2_12_12_1$, a = 5 180(3), b = 17.016(7), c = 31 37(1) Å, V = 2765 Å^3 D_c (Z = 4) = 1 18 g cm^{-3}, F(000) = 1056 μ_{Mo} = 0 5cm^{-1}, specimen 0 45 x 0 28 x 0 22 mm $2\theta_{max}$ = 45°, N = 1799, N_o = 1264; R = 0 082, R_w = 0 098 (n_w = 4)

Abnormal features/variation in procedure Nicely formed crystals of **(21)** nevertheless gave unusually wide line widths which, in conjunction with the long cell axis, caused resolution difficulties, resolved by the use of an ω-scan data collection mode with appropriate slit width Thermal motion in the structure is exceedingly high, particularly in the pendant substituents and is considered the chief contributing factor to the high residual

Table 2. Non-hydrogen atom co-ordinates

		(18)				(21)	
Atom	*x*	*y*	*z*	Atom	*x*	*y*	*z*
C(1)	0 7264(2)	0.2093(2)	0 0623(4)	C(11)	1 020(2)	0.4877(7)	0.1698(4)
C(2)	0 6823(2)	0 1981(2)	-0 0693(4)	C(12)	1 052(3)	0.4046(7)	0 1832(3)
C(21)	0 6582(2)	0.2660(2)	-0 1389(4)	C(1)	0 776(2)	0.5065(5)	0.1431(3)
C(22)	0 6136(2)	0.2649(2)	-0.2675(4)	C(2)	0 744(2)	0.4577(5)	0.1052(3)
O(22)	0.5823(2)	0 2051(2)	-0.3192(3)	C(21)	0.589(2)	0.3983(6)	0 1046(3)
O(23)	0 6104(2)	0 3437(2)	-0.3189(3)	C(22)	0 528(3)	0 3423(7)	0 0689(4)
C(23)	0 5681(3)	0 3545(3)	-0 4477(6)	O(22)	0.597(2)	0 3435(5)	0 0338(2)
C(24)	0 5504(3)	0 4440(4)	-0 4629(6)	O(23)	0.347(2)	0.2867(4)	0.0834(2)
C(3)	0 6682(2)	0 1064(2)	-0 1082(4)	C(23)	0.268(3)	0.2299(7)	0 0545(4)
C(4)	0 6338(2)	0 0560(2)	0 0103(4)	C(24)	0.129(4)	0 1728(8)	0 0769(4)
C(4a)	0 6802(2)	0 0639(2)	0 1421(4)	C(3)	0 911(2)	0 4764(6)	0 0688(3)
C(4b)	0 6497(2)	0 0103(2)	0.2597(4)	C(4)	0 880(2)	0 5616(7)	0.0567(3)
C(5)	0 6211(2)	-0 0712(2)	0 2381(4)	C(4a)	0 922(2)	0 6170(7)	0.0948(3)
C(6)	0 5948(2)	-0 1220(2)	0 3434(5)	C(4b)	0 894(2)	0 7071(6)	0 0842(4)
C(7)	0 5968(2)	-0 0915(3)	0 4771(4)	C(5)	1 035(3)	0 7306(7)	0.0471(4)
O(7)	0 5738(2)	-0.1362(2)	0 5906(3)	C(6)	1 009(3)	0 8095(9)	0.0376(5)
C(71)	0 5487(3)	-0.2223(3)	0.5730(7)	C(7)	0 829(3)	0 8606(7)	0.0609(4)
C(8)	0 6259(2)	-0.0102(2)	0 5008(4)	O(7)	0 819(2)	0 9364(5)	0 0418(3)
C(8a)	0 6535(2)	0 0400(2)	0.3949(4)	C(71)	0 645(4)	0 9868(8)	0.0589(5)
C(9)	0 6884(2)	0 1264(2)	0 4300(4)	C(8)	0 719(3)	0 8332(7)	0 0956(4)
C(10)	0.7352(2)	0 1622(2)	0 3137(4)	C(8a)	0 749(2)	0 7557(6)	0 1079(4)
O(10)	0 7542(1)	0.2512(1)	0 3446(3)	C(9)	0 636(2)	0 7284(6)	0 1490(3)
C(101)	0 8182(2)	0 2647(2)	0 4125(4)	C(10)	0 741(2)	0 6526(6)	0 1647(3)
O(101)	0 8612(2)	0.2085(2)	0 4475(4)	O(10)	0.596(2)	0 6251(4)	0.2008(2)
C(102)	0 8356(2)	0 3567(2)	0 4384(4)	C(101)	0 666(2)	0 6571(7)	0 2399(3)
O(102)	0.7661(1)	0 4085(1)	0 4333(3)	O(101)	0 833(2)	0 6999(5)	0 2450(2)
C(103)	0 8897(2)	0 3982(3)	0 3358(4)	C(102)	0 491(3)	0 6190(7)	0 2754(3)
C(104)	0 9088(2)	0 4837(2)	0 4094(4)	O(102)	0 511(2)	0 6675(6)	0.3107(3)
C(105)	0 8635(2)	0 4787(2)	0 5463(4)	C(1021)	0 352(4)	0 7220(8)	0 3137(5)
C(106)	0 7823(2)	0 4838(2)	0 4983(4)	C(103)	0 603(2)	0 5389(8)	0.2858(3)
O(106)	0 7369(2)	0 5404(2)	0 5083(3)	C(104)	0.510(4)	0 4696(9)	0.2686(4)
C(107)	0 8684(2)	0 3815(2)	0 5805(4)	C(105)	0 602(5)	0 3953(9)	0 2806(5)
C(1051)	0 8849(3)	0 5435(3)	0 6554(5)	C(106)	0 804(3)	0 396(1)	0 3068(5)
C(1071)	0 9489(2)	0 3493(3)	0 6084(4)	C(107)	0 886(3)	0 467(1)	0 3287(5)
C(1072)	0 8172(3)	0 3550(3)	0 6996(4)	C(108)	0 791(3)	0 5304(9)	0 3167(5)
C(10a)	0 6896(2)	0 1590(2)	0 1801(4)	C(10a)	0 735(2)	0 5919(6)	0 1303(3)

Experimental

General General directions are given in Part 1.[1]

Materials (1*S*)-(-)-Camphanic acid was prepared in three steps from natural (+)-camphor. (+)-Camphor was oxidised to camphoric acid with nitric acid according to the procedure of Bredt[27] This was then converted to α-bromocamphoric anhydride according to the procedure of Meyer *et al*[28] Finally, treatment of α-bromocamphoric anhydride with potassium acetate in glacial acetic acid, according to the procedure of Lapworth and Lenton,[29] gave (1*S*)-(-)-camphanic acid. Racemic *O*-methylmandelic acid was resolved *via* the (-)-ephedrine salts according to the procedure of Neilson and Peters[30] The optical purity of the resolved (*R*)-(-)-*O*-methylmandelic acid was assessed by ^{1}H n m.r. spectroscopy at 80 MHz. Addition of *ca.* 5 mol% of tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato] europium (III) to a 10% $CDCl_3$ solution of the methylated (diazomethane) (-)-acid established, by comparison with the spectrum obtained with the methylated racemic acid (which displayed two well resolved signals for the C-2 methine proton), that the enantiomeric excess was greater than 99%

*Ethyl (*E*)-(4a*R**,10*R**,10a*R**)-10-Hydroxy-7-methoxy-3,4,4a,9,10,10a-hexahydrophenanthren-2(1H)-ylideneacetate* (**4**) *and Ethyl (*Z*)-(4a*R**,10*R**,10a*R**)-10-Hydroxy-7-methoxy-3,4,4a,9,10,10a-hexahydrophenanthren-2(1*H*)-ylideneacetate* (**5**) A solution of *n*-BuLi (18 4 ml, 1 63 *M* in hexane, 30 mmol) was added dropwise to a stirred solution of triethyl phosphonoacetate (5 9 ml, 30 mmol) in THF (100 ml) at 0° under an atmosphere of

Ar On warming to room temperature the ketone (**1**)[1] (5.00 g, 20 mmol) was added and the mixture was stirred for 2 hours. The reaction mixture was then diluted with CH_2Cl_2, washed with water, dried ($MgSO_4$) and the solvent was removed *in vacuo* The products were separated by radial chromatography (15% EtOAc/toluene), the (*E*) ester (**4**) being eluted first, followed by the (*Z*) ester (**5**) The (*E*) *ester* (**4**) (3.14 g, 49 %) crystallised from CH_2Cl_2/petrol, m.p 127-8°, Found: C, 72.33, H, 7 76%. $C_{19}H_{24}O_4$ requires C, 72 13, H, 7 65%, ^{1}H n m r (300 MHz, $CDCl_3$): δ 1 28 (t, *J* 7 Hz, 3H, $OCH_2C\underline{H}_3$), 1 37 (dddd, *J* 3 5, 13, 13, 13 Hz, 1H, H-4$_{ax}$), 1 53 (dddd, *J* 3 5, 10, 12, 12 Hz, 1H, H-10a), 1 97-2 09 (m, 2H, H-1$_{ax}$, H-3$_{ax}$), 2 52-2 64 (m, 2H, H-4$_{eq}$, H-4a), 2.80 (dd, *J* 10, 16 Hz, 1H, H-9$_{ax}$), 2 85 (ddd, *J* 2, 3 5, 12 Hz, 1H, H-1$_{eq}$), 3.14 (dd, *J* 6, 16 Hz, 1H, H-9$_{eq}$), 3 78 (s, 3H, OMe), 3 80 (m, $W_{h/2}$ 30 Hz, 1H, H-10), 4 06 (dm, *J* 14 Hz/$W_{h/2}$ 8 Hz, 1H, H-3$_{eq}$), 4 15 (q, *J* 7 Hz, 2H, $OC\underline{H}_2CH_3$), 5 73 (s, 1H, vinyl-H), 6.62 (d, *J* 2 5 Hz, 1H, H-8), 6 74 (dd, *J* 2 5, 8 5 Hz, 1H, H-6), 7 19 (d, *J* 8 5 Hz, 1H, H-5), ^{13}C n m r (75 5 MHz, $CDCl_3$) See Table 1, *m*/*z* 316 (65%, M$^+$), 298 (37), 269 (66), 252 (22), 225 (48), 224 (24), 223 (24), 211 (34), 210 (91), 209 (46), 188 (38), 185 (64), 175 (99), 172 (20), 171 (100), 159 (38), 135 (20), 91 (20).

The (*Z*) *ester* (**5**) (1 75 g, 27%) crystallised from ether/petrol, m.p 53-4°, Found C, 71 96, H, 7 81% $C_{19}H_{24}O_4$ requires C, 72 13, H, 7 65%, ^{1}H n m r (300 MHz, $CDCl_3$): δ 1 27 (t, *J* 7 Hz, 3H, $OCH_2C\underline{H}_3$), 1 41 (dddd, *J* 4, 13, 13, 13 Hz, 1H, H-4$_{ax}$), 1 49 (dddd, *J* 3, 10, 12, 12 Hz, 1H, H-10a), 1 71 (dd, *J* 12, 12 Hz, 1H, H-1$_{ax}$), 2 30-2.65 (m, 4H, H-3$_{eq}$, H-3$_{ax}$, H-4$_{eq}$, H-4a), 2 80 (dd, *J* 10, 16 Hz, 1H, H-9$_{ax}$), 3 17 (dd, *J* 6, 16 Hz, 1H, H-9$_{eq}$), 3 78 (s, 3H, OMe), 3.83 (ddd, *J* 6, 10, 10 Hz, 1H, H-10), 4 15 (q, *J* 7 Hz, 2H, $OC\underline{H}_2CH_3$), 4 41 (ddd, *J* 2, 3, 12 Hz, 1H, H-1$_{eq}$), 5 71 (s, 1H, vinyl-H), 6 63 (d, *J* 2 5 Hz, 1H, H-8), 6 73 (dd, *J* 2 5, 8 5 Hz, 1H, H-6), 7 16 (d, *J* 8 5 Hz, 1H, H-5), ^{13}C n m r (75 5 MHz, $CDCl_3$) See Table 1, *m*/*z* 316 (47%, M$^+$), 298 (29), 269 (64), 252 (27), 225 (30), 211 (29), 210 (79), 209 (39), 185 (62), 175 (46), 171 (100)

*2-(Dimethylamino)ethyl (*E*)-(4a*R**,10*R**,10a*R**)-10-Hydroxy-7-methoxy-3,4,4a,9,10,10a-hexahydrophenanthren-2(1*H*)-ylideneacetate* (**10**) A mixture of the ethyl ester (**4**) (500 mg, 1 6 mmol), dioxane (20 ml) and aqueous sodium hydroxide solution (20 ml, 1*M*) was stirred at 80° under an atmosphere of Ar for 1 hr The reaction mixture was then poured into water, acidified with concentrated HCl and extracted with EtOAc The extract was washed with water, sat NaCl, dried ($MgSO_4$) and the solvent was removed *in vacuo* To a solution of the resulting crude acid in CH_2Cl_2 (15 ml) was added triethylamine (560 µl, 4 0 mmol), dimethylaminoethanol (200 µl, 2 0 mmol) and 2-bromo-1-methylpyridinium iodide[8] (600 mg, 2 0 mmol) and the mixture was stirred at room temperature under an atmosphere of Ar for 20 hrs The reaction mixture was diluted with CH_2Cl_2, and was washed with dilute aqueous NH_3 solution, water, dried ($MgSO_4$) and the solvent was removed *in vacuo* Radial chromatography (10% MeOH/$CHCl_3$) gave the *ester* (**10**) (450 mg, 79% over two steps) as a solid, m p 106-8°, Found C, 70 09, H, 8 06, N, 3.86% $C_{21}H_{29}NO_4$ requires C, 70.17; H, 8 13, N, 3 90%, ^{1}H n m r (300 MHz, $CDCl_3$)· δ 1 37 (dddd, *J* 3 5, 13, 13, 13 Hz, 1H, H-4$_{ax}$), 1.53 (dddd, *J* 3 5, 10, 12, 12 Hz, 1H, H-10a), 1 97-2 10 (m, 2H, H-1$_{ax}$, H-3$_{ax}$), 2 29 (s, 6H, NMe_2), 2 51-2 65 (m, 4H, H-4$_{eq}$, H-4a, $OCH_2C\underline{H}_2N$), 2 80 (dd, *J* 10, 16 Hz, 1H, H-9$_{ax}$), 2 85 (dm, *J* 12 Hz/$W_{h/2}$ 6 Hz, 1H, H-1$_{eq}$), 3.15 (dd, *J* 6, 16 Hz, 1H, H-9$_{eq}$), 3 78 (s, 3H, OMe), 3 80 (ddd, *J* 6, 10, 10 Hz, 1H, H-10), 4 07 (dm, *J* 14 Hz/$W_{h/2}$ 8 Hz, 1H, H-3$_{eq}$), 4 20 (t, *J* 6 Hz, 2H, $OC\underline{H}_2CH_2N$), 5 78 (s, 1H, vinyl-H), 6 62 (d, *J* 2 5 Hz, 1H, H-8), 6 74 (dd, *J* 2 5, 8 5 Hz, 1H, H-6), 7 19 (d, *J* 8 5 Hz, 1H, H-5), ^{13}C n m r (75 5 MHz, $CDCl_3$) See Table 2, *m*/*z* 209 (3), 175 (1), 171 (2), 159 (1), 145 (1), 135 (1), 91 (1), 72 (12), 71 (100), 59 (3), 58 (91)

*2-(Dimethylamino)ethyl (Z)-(4a*R**,10*R**,10a*R**)-10-Hydroxy-7-methoxy-3,4,4a,9,10,10a-hexahydrophenanthren-2(1*H*)-ylideneacetate* (**11**) The (*Z*) ethyl ester (**5**) (500 mg, 1 6 mmol) was converted to the dimethylaminoethyl ester by a method similar to that described for the preparation of the (*E*) analogue (**10**) The *ester* (**11**) (390 mg, 69% over two steps) crystallised from CH_2Cl_2/petrol, m p 120-2°, Found C, 70 24, H, 8 20, N, 3 92% $C_{21}H_{29}NO_4$ requires C, 70 17, H, 8 13, N, 3 90%, ^{1}H n m r. (300 MHz, $CDCl_3$) δ 1 41 (dddd, *J* 4, 13, 13, 13 Hz, 1H, H-4$_{ax}$), 1 49 (dddd, *J* 3, 10, 12, 12 Hz, 1H, H-10a), 1 71 (dd, *J* 12, 12 Hz, 1H, H-1$_{ax}$), 2 28 (s, 6H, NMe_2), 2 25-2 67 (m, 6H, H-3$_{eq}$, H-3$_{ax}$, H-4$_{eq}$, H-4a, $OCH_2C\underline{H}_2N$), 2 77 (dd, *J* 10, 16 Hz, 1H, H-9$_{ax}$), 3 18 (dd, *J* 6, 16 Hz, 1H, H-9$_{eq}$), 3 78 (s, 3H, OMe), 3 80 (ddd, *J* 6, 10, 10 Hz, 1H, H-10), 4 14-4 28 (m, 2H, OCH_2CH_2N), 4 33 (ddd, *J* 2, 3, 12 Hz, 1H, H-1$_{eq}$), 5 73 (s, 1H, vinyl-H), 6 63 (d, *J* th water, dried (Na_2SO_4) and the solvent was removed *in vacuo* to give the THP ether derivative as a pale llow semi-solid.

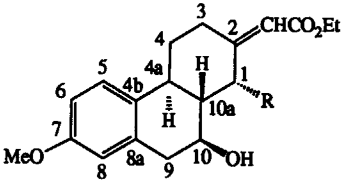
To a stirred solution of lithium diisopropylamide, prepared from diisopropylamine (2.2 ml, 16 mmol) and BuLi (8.1 ml, 1 88*M* in hexane, 15 mmol), in THF (50 ml) at -78° under an atmosphere of Ar, was added opwise ethyl (trimethylsilyl)acetate (2.8 ml, 15 mmol) The mixture was stirred at -78° for 0.5 hrs, then a lution of the above THP ether derivative in THF (30 ml) was added dropwise After stirring for 1 hr the iction mixture was allowed to warm to room temperature over 1 hr, and was then poured into 10% aqueous H_4Cl solution and extracted with CH_2Cl_2. The extract was washed with dilute HCl, water, dried ($MgSO_4$) and solvent was removed *in vacuo* The residue was dissolved in ethanol (60 ml) with pyridinium *p*-uenesulphonate (300 mg, 1 2 mmol) and the mixture was stirred at 65-70° (bath), under an atmosphere of Ar, 4 hrs The solution was cooled, poured into water and extracted with CH_2Cl_2. The extract was washed with iter, dried ($MgSO_4$) and the solvent was removed *in vacuo*. The products were separated by radial romatography (15% EtOAc/toluene), the (*E*) ester (**6**) being eluted first, followed by the (*Z*) ester (**7**) The (*E*) *er* (**6**) (1.64 g, 39% over three steps) crystallised from CH_2Cl_2/petrol, m p. 75-7°, Found. C, 72.72, H, 00% $C_{20}H_{26}O_4$ requires C, 72.70, H, 7 93%; ^{1}H n m r (300 MHz, $CDCl_3$). δ 1 17 (d, *J* 7 Hz, 3H, Me-, 1 22-1 37 (m, 4H, H-4_{ax}, $OCH_2C\underline{H}_3$), 1.65 (ddd, *J* 4, 11, 11 Hz, 1H, H-10a), 2.22 (dddd, *J* 1 5, 5, 13, Hz, 1H, H-3_{ax}), 2 54 (m, $W_{h/2}$ 24 Hz, 1H, H-4_{eq}), 2 78 (dd, *J* 10,16 Hz, 1H, H-9_{ax}), 2 88 (br dd, *J*≈11, Hz, 1H, H-4a), 2.97 (dq, *J* 4, 7 Hz, 1H, H-1), 3 10 (dd, *J* 5 5, 16 Hz, 1H, H-9_{eq}), 3.76 (s, 3H, OMe), 35-3 98 (m, 2H, H-3_{eq}, H-10), 4 15 (q, *J* 7 Hz, 2H, $OC\underline{H}_2CH_3$), 5 77 (d, *J* 1 5 Hz, 1H, vinyl-H), 6 59 (d, *J* 5 Hz, 1H, H-8), 6 73 (dd, *J* 2.5, 8 5 Hz, 1H, H-6), 7 18 (d, *J* 8.5 Hz, 1H, H-5); ^{13}C n.m r (75 5 MHz, Cl_3)· See Table 1, *m/z*: 330 (45%, M^+), 312 (19), 285 (16), 283 (54), 266 (28), 239 (36), 238 (17), 225)), 224 (36), 223 (28), 209 (24), 199 (21), 188 (21), 172 (19), 171 (100), 166 (20), 161 (16), 160 (15), 159 3), 147 (25), 146 (18), 145 (16), 135 (21)

The (*Z*) *ester* (**7**) (0.88 g, 21% over three steps) was obtained as a gum, Found. C, 72 72, H, 8 07% $_0H_{26}O_4$ requires C, 72 70, H, 7.93%, ^{1}H n m r (300 MHz, $CDCl_3$). δ 1.18 (d, *J* 7 Hz, 3H, Me-2), 1.28 (t, Hz, 3H, $OCH_2C\underline{H}_3$), 1 35 (m, $W_{h/2}$ 40 Hz, 1H, H-4_{ax}), 1 60 (ddd, *J* 4, 10, 11 Hz, 1H, H-10a), 2.25 (dm, 13 Hz/$W_{h/2}$ 7 Hz, 1H, H-3_{eq}), 2 50-2.69 (m, 2H, H-3_{ax}, H-4_{eq}), 2.80 (dd, *J* 10, 16 Hz, 1H, H-9_{ax}), 2.89 (br , *J*≈11, 11 Hz, 1H, H-4a), 3.13 (dd, *J* 5, 16 Hz, 1H, H-9_{eq}), 3 77 (s, 3H, OMe), 3 97 (ddd, *J* 5, 10, 10 Hz, I, H-10), 4.14 (q, *J* 7 Hz, 2H, $OC\underline{H}_2CH_3$), 4.52 (dq, *J* 4, 7 Hz, 1H, H-1), 5 64 (d, *J* 1.5 Hz, 1H, vinyl-H), 51 (d, *J* 2 5 Hz, 1H, H-8), 6 75 (dd, *J* 2 5, 8 5 Hz, 1H, H-6), 7 18 (d, *J* 8.5 Hz, 1H, H-5), ^{13}C n m r 5 5 MHz, $CDCl_3$)· See Table 1, *m/z* 330 (41%, M^+), 312 (28), 283 (50), 237 (20), 225 (21), 224 (49), 223 4), 209 (29), 199 (32), 176 (27), 175 (45), 172 (22), 171 (100), 165 (34), 159 (24), 145 (23)

*Dimethylamino)ethyl (*E*)-(1R*,4aS*,10S*,10aS*)-10-Hydroxy-7-methoxy-1-methyl-3,4,4a,9,10,10a-hexadrophenanthren-2(1*H*)-ylideneacetate* (**12**) The (*E*) ethyl ester (**6**) (500 mg, 1 52 mmol) was converted to dimethylaminoethyl ester by a method similar to that described for the preparation of the (*E*) analogue (**10**) rification by radial chromatography (10% MeOH/$CHCl_3$) gave the *ester* (**12**) (454 mg, 80% over two steps) as gum, Found C, 70.97, H, 8 29, N, 3 78% $C_{22}H_{31}NO_4$ requires C, 70 75, H, 8 37, N, 3 75%, ^{1}H n m r 00 MHz, $CDCl_3$) δ 1 17 (d, *J* 7 Hz, 3H, Me-1), 1 28 (dddd, *J* 4, 13, 13, 13 Hz, 1H, H-4_{ax}), 1 65 (ddd, *J* 4, , 11 Hz, 1H, H-10a), 2 22 (dddd, *J* 1.5, 5, 13, 13 Hz, 1H, H-3_{ax}), 2 30 (s, 6H, NMe_2), 2 50-2.63 (m, 3H, 4_{eq}, $OCH_2C\underline{H}_2N$), 2 78 (dd, *J* 10, 16 Hz, 1H, H-9_{ax}), 2 88 (br dd, *J*≈11, 11 Hz, 1H, H-4a), 2 97 (dq, *J* 4, Hz, 1H, H-1), 3 10 (dd, *J* 5 5, 16 Hz, 1H, H-9_{eq}), 3 76 (s, 3H, OMe), 3.85-3.98 (m, 2H, H-3_{eq}, H-10), 15-4 26 (m, 2H, $OC\underline{H}_2CH_2N$), 5 82 (d, *J* 1 5 Hz, 1H, vinyl-H), 6 59 (d, *J* 2 5 Hz, 1H, H-8), 6 73 (dd, *J* 5, 8 5 Hz, 1H, H-6), 7 18 (d, *J* 8 5 Hz, 1H, H-5), ^{13}C n m r. (75.5 MHz, $CDCl_3$) See Table 2, *m/z* 223), 175 (1), 171 (2), 159 (1), 135 (1), 72 (9), 71 (77), 59 (3), 58 (100)

(Dimethylamino)ethyl (Z)-(1R,4aS*,10S*,10aS*)-10-Hydroxy-7-methoxy-1-methyl-3,4,4a,9,10,10a-hexadrophenanthren-2(1*H*)-ylideneacetate* (**13**) The (*Z*) ethyl ester (**7**) (670 mg, 2 03 mmol) was converted to the methylaminoethyl ester by a method similar to that described for the preparation of the (*E*) analogue (**10**) rification by radial chromatography (10% MeOH/$CHCl_3$) gave the *ester* (**13**) (504 mg, 67% over two steps) as solid, m.p 120-1°, Found C, 70 61, H, 8 22, N, 3 61% $C_{22}H_{31}NO_4$ requires C, 70 75, H, 8 37, N, 75%, ^{1}H n m r. (300 MHz, $CDCl_3$) δ 1 16 (d, *J* 7 Hz, 3H, Me-2), 1 35 (m, $W_{h/2}$ 40 Hz, 1H, H-4_{ax}), 1 60 dd, *J* 4, 10, 11 Hz, 1H, H-10a), 2 25 (dm, *J* 13 Hz/$W_{h/2}$ 7 Hz, 1H, H-3_{eq}), 2 29 (s, 6H, NMe_2), 2 50-2 69 ı, 4H, H-3_{ax}, H-4_{eq}, $OCH_2C\underline{H}_2N$), 2 77 (dd, *J* 10, 16 Hz, 1H, H-9_{ax}), 2 89 (br dd, *J*≈11, 11 Hz, 1H, H-), 3 13 (dd, *J* 5, 16 Hz, 1H, H-9_{eq}), 3 77 (s, 3H, OMe), 3 92 (ddd, *J* 5, 10, 10 Hz, 1H, H-10), 4.13-4 27 ı, 2H, $OC\underline{H}_2CH_2N$), 4 47 (dq, *J* 4, 7 Hz, 1H, H-1), 5 66 (d, *J* 1 5 Hz, 1H, vinyl-H), 6 60 (d, *J* 2 5 Hz, 1H, 8), 6 73 (dd, *J* 2 5, 8 5 Hz, 1H, H-6), 7 17 (d, *J* 8 5 Hz, 1H, H-5), ^{13}C n.m r (75 5 MHz, $CDCl_3$) See ıble 2, *m/z* 223 (1), 171 (2), 163 (1), 159 (1), 135 (1), 121 (1), 72 (13), 71 (90), 59 (4), 58 (100)

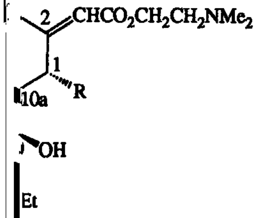
Table 1



R = H, Me, Et

Carbon	(4)	(5)	(6)	(7)	(8)	(9)
1	39.5	31.5	39.6	30.3	47.3	37.0
2	160.5	160.4	165.8	165.6	163.4	163.8
3	28.9	37.1	24.4	33.2	24.5	33.6
4	31.5	32.3	32.6	32.7	32.9	32.8
4a	41.6	41.8	34.8	34.8	35.6	35.3
4b	130.5	130.6	130.8	130.8	131.0	130.9
5	126.5	126.2	127.1	126.9	127.1	126.8
6	112.3	112.4	112.4	112.5	112.5	112.4
7	157.8	158.0	157.8	157.8	157.8	157.7
8	113.7	113.8	113.6	113.5	113.6	113.5
8a	135.7	136.2	135.3	135.8	135.3	135.8
9	39.9	39.8	40.4	40.2	40.6	40.4
10	71.3	71.4	67.6	67.6	67.5	67.5
10a	49.1	48.7	50.8	50.2	51.8	51.2
OMe	55.2	55.3	55.2	55.2	55.2	55.2
$\underline{C}HCO_2$	114.4	114.3	113.6	113.5	115.2	115.5
$\underline{C}O_2$	166.8	166.7	167.0	166.4	166.7	166.6
Me-1	-	-	13.5	12.5	-	-
$CH_2\underline{C}H_3$	-	-	-	-	12.1	11.3
$\underline{C}H_2CH_3$	-	-	-	-	18.7	19.0
$OCH_2\underline{C}H_3$	14.3	14.3	14.3	14.3	14.3	14.2
$O\underline{C}H_2CH_3$	59.7	59.7	59.6	59.6	59.6	59.6

Table 2



(12)	(13)	(14)	(15)
39.6	30.6	47.3	37.5
166.5	165.7	164.3	163.9
24.4	33.3	24.5	33.8
32.6	32.6	32.8	32.6
34.8	34.7	35.6	35.3
130.8	130.7	130.9	130.9
127.1	126.9	127.0	126.8
112.4	112.4	112.4	112.3
157.8	157.7	157.7	157.7
113.4	113.4	113.5	113.5
135.4	135.9	135.4	135.9
40.4	40.3	40.6	40.6
67.4	67.4	67.3	67.4
50.8	50.4	51.8	51.4
55.2	55.2	55.2	55.1
113.6	113.5	114.9	115.3
166.9	166.4	166.5	166.6
13.4	12.4	-	-
-	-	12.0	11.4
-	-	18.6	18.8
57.7	57.8	57.7	57.8
61.2	61.0	61.3	60.9
45.6	45.6	45.6	45.4

Ethyl (E)*-(1*R**,4a*S**,10*S**,10a*S**)-1-Ethyl-10-hydroxy-7-methoxy-3,4,4a,9,10,10a-hexahydrophenanthren-2(1*H*)-ylideneacetate* (**8**) *and Ethyl* (Z)*-(1*R**,4a*S**,10*S**,10a*S**)-1-Ethyl-10-Hydroxy-7-methoxy-3,4,4a,9,10, 10a-hexahydrophenanthren-2(1*H*)-ylideneacetate* (**9**). The ketone (**3**)[1] (4.6 g, 16.8 mmol) was converted to the *E* and *Z* esters, (**8**) and (**9**), according to the procedure described for the preparation of (**6**) and (**7**) The products were separated by radial chromatography (15% EtOAc/toluene), the (*E*) ester (**8**) being eluted first, followed by the (*Z*) ester (**9**) The (*E*) *ester* (**8**) (1.23 g, 21% over three steps) crystallised from CH_2Cl_2/petrol, m p 125-125.5°, Found. C, 73.21, H, 7.96% $C_{21}H_{28}O_4$ requires C, 73 23, H, 8 19%; ^{1}H n m.r (300 MHz, $CDCl_3$) δ 0 86 (dd, *J* 7 5, 7.5 Hz, 3H, C(H)HC$\underline{H}_3$), 1.29 (t, *J* 7 Hz, 3H, $OCH_2C\underline{H}_3$), 1 33 (dddd, *J* 3 5, 13, 13, 13 Hz, 1H, H-4$_{ax}$), 1 57 (ddq, *J* 11.5, 13, 7 5 Hz, 1H, C($\underline{H}$)HCH_3), 1 62-1.77 (m, 2H, H-10a, C(H)$\underline{H}CH_3$), 2.10 (dddd, *J* 1.5, 5, 13, 13 Hz, 1H, H-3$_{ax}$), 2 55 (m, W$_{h/2}$ 24 Hz, 1H, H-4$_{eq}$), 2 64 (ddd, *J* 4, 4, 11 5 Hz, 1H, H-1), 2 79 (dd, *J* 10, 16 Hz, 1H, H-9$_{ax}$), 2.90 (ddd, *J* 3, 11, 13 Hz, 1H, H-4a), 3 10 (dd, *J* 5, 16 Hz, 1H, H-9$_{eq}$), 3 77 (s, 3H, OMe), 3 95 (dm, *J* 13 Hz,W$_{h/2}$ 8 Hz, 1H, H-3$_{eq}$), 4.02 (ddd, *J* 5, 10, 10 Hz, 1H, H-10), 4.16 (q, *J* 7 Hz, 2H, $OC\underline{H}_2CH_3$), 5 73 (d, *J* 1 5 Hz, 1H, vinyl-H), 6.60 (d, *J* 2 5 Hz, 1H, H-8), 6 74 (dd, *J* 2 5, 8 5 Hz, 1H, H-6), 7 19 (d, *J* 8 5 Hz, 1H, H-5), ^{13}C n m.r (75.5 MHz, $CDCl_3$)· See Table 1, *m/z* 344 (35%, M$^+$), 326 (16), 299 (16), 297 (61), 280 (23), 253 (35), 223 (33), 209 (29), 190 (16), 188 (27), 180 (28), 175 (61), 172 (28), 171 (100), 163 (19), 161 (17), 160 (15), 159 (25), 147 (24), 146 (21), 135 (23)

The (*Z*) *ester* (**9**) (2 55 g, 44% over three steps) was obtained as a gum; Found. C, 72 97, H, 8 20% $C_{21}H_{28}O_4$ requires C, 73 23, H, 8.19%, ^{1}H n.m r (300 MHz, $CDCl_3$)· δ 0 87 (dd, *J* 7.5, 7 5 Hz, 3H, C(H)HC$\underline{H}_3$), 1.27 (t, *J* 7Hz, 3H, $OCH_2C\underline{H}_3$), 1.36 (m, W$_{h/2}$ 45 Hz, 1H, H-4$_{ax}$), 1.55 (ddq, *J* 11 5, 13, 7.5 Hz, 1H, C($\underline{H}$)HCH_3), 1.64 (ddd, *J* 4, 10, 11 Hz, 1H, H-10a), 1.76 (ddq, *J* 4, 13, 7.5 Hz, C(H)$\underline{H}CH_3$), 2.22 (m, W$_{h/2}$ 20 Hz, 1H, H-3$_{eq}$), 2 47-2.61 (m, 2H, H-3$_{ax}$, H-4$_{eq}$), 2.78 (dd, *J* 10, 16 Hz, 1H, H-9$_{ax}$), 2 91 (br dd, *J*≈11, 11 Hz, 1H, H-4a), 3.12 (dd, *J* 5, 16 Hz, 1H, H-9$_{eq}$), 3.77 (s, 3H, OMe), 4.00 (ddd, *J* 5, 10, 10 Hz, 1H, H-10), 4.13 (q, *J* 7 Hz, 2H, $OC\underline{H}_2CH_3$), 4 43 (ddd, *J* 4, 4, 11 5 Hz, 1H, H-1), 5 77 (d, *J* 1 Hz, 1H, vinyl-H), 6 60 (d, *J* 2 5 Hz, 1H, H-8), 6.73 (dd, *J* 2 5, 8 5 Hz, 1H, H-6), 7.16 (d, *J* 8 5 Hz, 1H, H-5), ^{13}C n m r (75.5 MHz, $CDCl_3$) See Table 1, m/z 344 (30%, M$^+$), 326 (23), 299 (18), 298 (16), 297 (62), 253 (27), 251 (17), 239 (15), 238 (19), 223 (41), 213 (38), 209 (34), 190 (18), 188 (30), 179 (35), 175 (50), 172 (30), 171 (100), 159 (24), 146 (16), 135 (20)

2-(Dimethylamino)ethyl (E)*-(1*R**,4a*S**,10*S**,10a*S**)-1-Ethyl-10-hydroxy-7-methoxy-3,4,4a,9,10,10a-hexahydrophenanthren-2(1*H*)-ylideneacetate* (**14**). The (*E*) ethyl ester (**8**) (350 mg, 1 02 mmol) was converted to the dimethylaminoethyl ester by a method similar to that described for the preparation of the (*E*) analogue (**10**). Purification by radial chromatography (10% MeOH/$CHCl_3$) gave the *ester* (**14**) (380mg, 97% over two steps) as a gum, Found C, 71 50; H, 8.52, N, 3 67% $C_{23}H_{33}NO_4$ requires C, 71 29; H, 8 58; N, 3 61%, ^{1}H n m r (300 MHz, $CDCl_3$) δ 0.83 (dd, *J* 7.5, 7.5 Hz, 3H, C(H)HC$\underline{H}_3$), 1 30 (dddd, *J* 3.5, 13, 13, 13 Hz, 1H, H-4$_{ax}$), 1.55 (ddq, *J* 11 5, 13, 7 5 Hz, 1H, C($\underline{H}$)HCH_3), 1 60-1 75 (m, 2H, H-10a, C(H)$\underline{H}CH_3$), 2.09 (dddd, *J* 1 5, 5, 13, 13 Hz, 1H, H-3$_{ax}$), 2.29 (s, 6H, NMe_2), 2 53 (m, W$_{h/2}$ 24 Hz, 1H, H-4$_{eq}$), 2 60 (apparent t, *J* 5 Hz, 2H, $OCH_2C\underline{H}_2N$), 2 63 (ddd, *J* 4, 4, 11.5 Hz, 1H, H-1), 2 77 (dd, *J* 10, 16 Hz, 1H, H-9$_{ax}$), 2 88 (ddd, *J* 3, 11, 13 Hz, 1H, H-4a), 3.07 (dd, *J* 5, 16 Hz, 1H, H-9$_{eq}$), 3.75 (s, 3H, OMe), 3 92 (dm, *J* 13 Hz/W$_{h/2}$ 8 Hz, 1H, H-3$_{eq}$), 3 97 (ddd, *J* 5, 10, 10 Hz, 1H, H-10), 4.13-4 26 (m, 2H, $OCH_2C\underline{H}_2N$), 5 78 (d, *J* 1 5 Hz, 1H, vinyl-H), 6 58 (d, *J* 2 5 Hz, 1H, H-8), 6.72 (dd, *J* 2 5, 8 5 Hz, 1H, H-6), 7 17 (d, *J* 8 5 Hz, 1H, H-5), ^{13}C n m r (75 5 MHz, $CDCl_3$) See Table 2, *m/z*. 175 (1), 171 (2), 163 (1), 145 (1), 135 (1), 72 (9), 71 (96), 59 (4), 58 (100)

2-(Dimethylamino)ethyl (Z)*-(1*R**,4a*S**,10*S**,10a*S**)-1-Ethyl-10-hydroxy-7-methoxy-3,4,4a,9,10,10a-hexahydrophenanthren-2(1*H*)-ylideneacetate* (**15**) The (*Z*) ethyl ester (**9**) (500 mg, 1 45 mmol) was converted to the dimethylaminoethyl ester by a method similar to that described for the preparation of the (*E*) analogue (**10**) Purification by radial chromatography (10% MeOH/$CHCl_3$) gave the *ester* (**15**) (390 mg, 69% over two steps) as a solid, m p. 97-9°, Found· C, 71 31, H, 8 40, N, 3.56%. $C_{23}H_{33}NO_4$ requires C, 71 29, H, 8 58, N, 3 61%, ^{1}H n m r. (300 MHz, $CDCl_3$). δ 0.85 (dd, *J* 7 5, 7 5 Hz, 3H, C(H)HC$\underline{H}_3$), 1 33 (m, W$_{h/2}$ 45 Hz, 1H, H-4$_{ax}$), 1 55 (ddq, *J* 11 5, 13, 7.5 Hz, 1H, C($\underline{H}$)HCH_3), 1 62 (ddd, *J* 4, 10, 11 Hz, 1H, H-10a), 1 75 (ddq, *J* 4, 13, 7 5 Hz, C(H)$\underline{H}CH_3$), 2 22 (m, W$_{h/2}$ 20 Hz, 1H, H-3$_{eq}$), 2 28 (s, 6H, NMe_2), 2 46-2 62 (m, 4H, H-3$_{ax}$, H-4$_{eq}$, $OCH_2C\underline{H}_2N$), 2 75 (dd, *J* 10, 16 Hz, 1H, H-9$_{ax}$), 2 90 (br dd, *J*≈11, 11 Hz, 1H, H-4a), 3 12 (dd, *J* 5, 16 Hz, 1H, H-9$_{eq}$), 3.75 (s, 3H, OMe), 3 95 (ddd, *J* 5, 10, 10 Hz, 1H, H-10), 4 12-4 25 (m, 2H, $OC\underline{H}_2CH_2N$), 4 35 (ddd, *J* 4, 4, 11 5 Hz, 1H, H-1), 5 78 (d, *J* 1 Hz, 1H, vinyl-H), 6 59 (d, *J* 2 5 Hz, 1H, H-8), 6 71 (dd, *J* 2 5, 8 5 Hz, 1H, H-6), 7 14 (d, *J* 8 5 Hz, 1H, H-5), ^{13}C n m r (75 5 MHz, $CDCl_3$) See Table 2, *m/z* 171 (2), 163 (1), 73 (1), 72 (15), 71 (99), 59 (4), 58 (100)

Optical Resolution of Ethyl (E)*-(4a*R**,10*R**,10a*R**)-10-Hydroxy-7-methoxy-3,4,4a,9,10,10a-hexahydrophenanthren-2(1*H*)-ylideneacetate* (**4**) Oxalyl chloride (750 μl, 8 6 mmol) was added dropwise to a solution of DMF (700 μl, 9 0 mmol) in CH_2Cl_2 (25 ml) at 0° under an atmosphere of Ar After stirring for 5 min, (1*S*)-(-)-

camphanic acid (1.54 g, 7.8 mmol) was added and the mixture was stirred for a further 5 min. A solution of the alcohol (**4**) (2.5 g, 7.9 mmol) in dry pyridine (5 ml) was then added dropwise; the mixture was allowed to warm to room temperature and was stirred for 1 hr. The reaction mixture was then diluted with CH_2Cl_2, washed with cold dilute HCl, water, dried ($MgSO_4$) and the solvent was removed *in vacuo*. Radial chromatography (25% EtOAc/petrol) gave the mixture of diastereomeric camphanates (3 44 g, 88%) as a semi-solid. Fractional crystallisation from CH_2Cl_2/petrol gave the *(4aS,10S,10aS)-camphanate* (**18**) (1 43 g, 36%) with 100% d e by h p.l.c. analysis (5% EtOAc/petrol, 7 0 ml min^{-1}, R_t 20 8 min), m.p. 187.5-8.5°, $[\alpha]_D$ = -20.0° (c = 1 15, $CHCl_3$); Found· C, 69.97; H, 7.25% $C_{29}H_{32}O_7$ requires C, 70 14; H, 7.31%, ^1H n.m.r. (300 MHz, $CDCl_3$)· δ 1.02, 1.10, 1.15 (3 x s, each 3H, Me-4', 2 x Me-7'), 1 28 (t, *J* 7 Hz, 3H, $OCH_2C\underline{H}_3$), 1.39 (dddd, *J* 3.5, 13, 13, 13 Hz, 1H, H-4_{ax}), 1.67-2.13 (m, 6H, H-1_{ax}, H-3_{ax}, H-10a, $\{H\text{-}5'\}_2$, H-$6'_{endo}$), 2 47 (ddd, *J* 4.5, 10.5, 13 5 Hz, 1H, H-$6'_{exo}$), 2 58-2.73 (m, 3H, H-1_{eq}, H-4_{eq}, H-4a), 2 88 (dd, *J* 10, 16 Hz, 1H, H-9_{ax}), 3.23 (dd, *J* 6, 16 Hz, 1H, H-9_{eq}), 3.77 (s, 3H, OMe), 4 08 (dm, *J* 14 Hz/$W_{h/2}$ 7 Hz, 1H, H-3_{eq}), 4 15 (q, *J* 7 Hz, 2H, $OC\underline{H}_2CH_3$), 5.15 (ddd, *J* 6, 10, 10 Hz, 1H, H-10), 5 72 (s, 1H, vinyl-H), 6.60 (d, *J* 2 5 Hz, 1H, H-8), 6.76 (dd, *J* 2.5, 8.5 Hz, 1H, H-6), 7.20 (d, *J* 8.5 Hz, 1H, H-5), ^{13}C n m r. (75.5 MHz, $CDCl_3$)· δ 9 7 (Me-4'), 14 3 ($OCH_2\underline{C}H_3$), 16.8, 16.9 (2 x Me-7'), 28 7* (C-6'), 28 9 (C-3), 30.8* (C-5'), 31 3 (C-4), 35 9 (C-1), 39.4 (C-9), 41.4 (C-4a), 45 9 (C-10a), 54.2, 54.8 (C-4', C-7'), 55.2 (OMe), 59 7 ($O\underline{C}H_2CH_3$), 75 1 (C-10), 91.0 (C-1'), 112.7 (C-6), 113.6 (C-8), 115 0 ($\underline{C}HCO_2Et$), 126.5 (C-5), 129.8 (C-4b), 134.5 (C-8a), 158.1 (C-7), 159.1 (C-2), 166.5 ($\underline{C}O_2Et$), 167.3 (C-3'), 178.2 (OC(O)-1'), *m/z*: 299 (8), 298 (27), 269 (8), 225 (11), 224 (12), 211 (9), 210 (23), 185 (13), 172 (15), 171 (100)

*(4a*R*,10*R*,10a*R*)-*O*-Methylmandelate* (**17**) The mother liquor from the fractional crystallisation of the (4a*S*,10*S*,10a*S*)-camphanate (**18**) was concentrated *in vacuo* to give an oil (1 73 g), which by h p l c analysis had an 86% d e of the (4a*R*,10*R*,10a*R*)-camphanate (**19**) (R_t 24.0 min) The oil was then dissolved in anhydrous ethanol (40 ml) with anhydrous K_2CO_3 (800 mg) and the mixture was heated under reflux for 2 hrs under an atmosphere of Ar The solution was then cooled, poured into water, and extracted with CH_2Cl_2 The extract was washed with water, dried ($MgSO_4$) and the solvent was removed *in vacuo* Radial chromatography (30% EtOAc/petrol) gave the optically enriched alcohol (760 mg, 2 4 mmol) as a solid. The alcohol was then esterified with (*R*)-(-)-*O*-methylmandelic acid (480 mg, 2 9 mmol) using oxalyl chloride/DMF, according to the procedure described for the preparation of the camphanate (**18**) Radial chromatography (30% EtOAc/petrol) gave the mixture of diastereomeric *O*-methylmandelates (1 06 g) as an oil H.p.l c. analysis (5% EtOAc/petrol, 5 0 ml min^{-1}) indicated an 86% d e of the (4a*R*,10*R*,10a*R*)-*O*-methylmandelate (**17**) (R_t 13 1 min, (4a*S*,10*S*,10a*S*)-*O*-methylmandelate (**16**), R_t 11.8 min) Fractional crystallisation from ether/petrol gave the *(4a*R*,10*R*,10a*R*)-*O*-methylmandelate* (**17**) (870 mg, 24% from initial racemic alcohol (**4**)) with 100% d e by h p l c analysis, m.p 120-1°, $[\alpha]_D$ = -15 0° (c = 1 36, $CHCl_3$), Found· C, 72 28, H, 7 09% $C_{28}H_{32}O_6$ requires C, 72 39, H, 6 94%; ^1H n.m.r. (300 MHz, $CDCl_3$). δ 1 19-1 34 (m, 4H, H-4_{ax}, $OCH_2C\underline{H}_3$), *ca* 1 60 (m, 1H, H-10), 1 65-1 75 (m, 2H, H-1_{ax}, H-1_{eq}), 1 90 (ddd, *J* 4, 13, 13 Hz, 1H, H-3_{ax}), 2 50-2 61 (m, 2H, H-4_{eq}, H-4a), 2 84 (dd, *J* 10, 16 Hz, 1H, H-9_{ax}), 3 21 (dd, *J* 6, 16 Hz, 1H, H-9_{eq}), 3 44 (s, 3H, C2'-OMe), 3 76 (s, 3H, OMe), 3 94 (dm, *J* 14 Hz/$W_{h/2}$ 7 Hz, 1H, H-3_{eq}), 4 14 (q, *J* 7 Hz, 2H, $OC\underline{H}_2CH_3$), 4 80 (s, 1H, H-2'), 5.02 (ddd, *J* 6, 10, 10 Hz, 1H, H-10), 5 22 (s, 1H, vinyl-H), 6 57 (d, *J* 2 5 Hz, 1H, H-8), 6 73 (dd, *J* 2 5, 8.5 Hz, 1H, H-6), 7 13 (d, *J* 8 5 Hz, 1H, H-5), 7 38-7 51(m, 5H, ArH"); ^{13}C n m.r (75 5 MHz, $CDCl_3$) δ 14 3 ($OCH_2\underline{C}H_3$), 28 7 (C-3), 31.3 (C-4), 35 9 (C-1), 38 5 (C-9), 41 3 (C-4a), 46 2 (C-10a), 55 2 (OMe), 57 2 (2'-OMe), 59 6 ($O\underline{C}H_2CH_3$), 73 9 (C-10), 82 5 (C-2'), 112 5 (C-6), 113 7 (C-8), 114 6 ($\underline{C}HCO_2Et$), 126 4 (C-5), 127 4 (C-2", C-6"), 128 8 (C-3", C-5"), 129 0 (C-4"), 129 8 (C-4b), 134 7 (C-1"), 136 5 (C-8a), 158.0 (C-7), 159 4 (C-2), 166 6 ($\underline{C}O_2Et$), 170 3 (C-1'), m/z 299 (9), 298 (43), 210 (10), 172 (8), 171 (44), 122 (10), 121 (100)

*Ethyl (*E*)-(4aS,10S,10aS)-10-Hydroxy-7-methoxy-3,4,4a,9,10,10a-hexahydrophenanthren-2(1*H*)-ylideneacetate* (+)-(**4**) The (4a*S*,10*S*,10a*S*)-camphanate (**18**) (1 00 g, 2 0 mmol) was converted to the alcohol (+)-(**4**) according to the procedure described for the preparation of the *O*-methylmandelate (**17**) Radial chromatography (30% EtOAc/petrol) gave the *alcohol* (+)-(**4**) (450 mg, 71%) which crystallised from CH_2Cl_2/petrol, m p 89-90°, $[\alpha]_D$ = +8.2° (c = 0.975, $CHCl_3$)

*(4aS,10S,10aS)-*O*-Methylmandelate* (**16**) Oxalyl chloride (27 µl, 0 31 mmol) was added dropwise to a solution of DMF (27 µl, 0.35 mmol) in CH_2Cl_2 (1 ml) at 0° under an atmosphere of Ar After stirring for 5 min, (1*R*)-(-)-*O*-methylmandelic acid (53 mg, 0 32 mmol) was added and the mixture was stirred for a further 5 min A solution of the alcohol (+)-(**4**) (20 mg, 0 06 mmol) in dry pyridine (200 µl) was then added dropwise, the mixture was allowed to warm to room temperature and was stirred for 1 hr A few drops of water were then added to the reaction and the mixture stirred at room temperature for 30 min The reaction mixture was then diluted with CH_2Cl_2, washed with cold dilute HCl, sat $NaHCO_3$, water, dried ($MgSO_4$) and the solvent was removed *in vacuo*. The crude product was then examined by ^1H n m.r spectroscopy, ^1H n m r (300 MHz, $CDCl_3$) δ 1 29 (t, *J* 7 Hz, 3H, $OCH_2C\underline{H}_3$), 1 35 (dddd, *J* 3 5, 13, 13, 13 Hz, 1H, H-4_{ax}), 1.71 (dddd, *J* 3 5, 10, 12, 12 Hz, 1H, H-10a), 1 95 (dd, *J* 12, 12 Hz, 1H, H-1_{ax}), 1.99 (br dd, *J*≈13, 13 Hz, 1H, H-3_{ax}), 2 40

$W_{h/2}$ 6 Hz, 1H, H-1_{eq}), 2 55-2 67 (m, 2H, H-4_{eq}, H-4a), 2.65 (dd, *J* 10, 16 Hz, 1H, H-9_{ax}),
16 Hz, 1H, H-9_{eq}), 3 46 (s, 3H, C2'-OMe), 3.74 (s, 3H, OMe), 4 03 (dm, *J* 14 Hz/$W_{h/2}$ 7 Hz,
16 (q, *J* 7 Hz, 2H, $OC\underline{H}_2CH_3$), 4.83 (s, 1H, H-2'), 5.06 (ddd, *J* 6, 10, 10 Hz, 1H, H-10), 5 61
), 6.49 (d, *J* 2 5 Hz, 1H, H-8), 6.72 (dd, *J* 2 5, 8.5 Hz, 1H, H-6), 7 16 (d, *J* 8.5 Hz, 1H, H-
m, 5H, ArH")

*,10*R*,10a*R*)-10-Hydroxy-7-methoxy-3,4,4a,9,10,10a-hexahydrophenanthren-2(1*H*)-ylidene-*
The (4a*R*,10*R*,10a*R*)-*O*-methylmandelate (**17**) (750 mg, 1.6 mmol) was dissolved in anhydrous
) with anhydrous K_2CO_3 (600 mg) and the mixture was stirred at 60° (bath) for 2.5 hrs under an
Ar. The solution was cooled, poured into water, and extracted with CH_2Cl_2. The extract was
ater, dried ($MgSO_4$) and the solvent was removed *in vacuo* Radial chromatography (30%
gave the *alcohol* (-)-(**4**) (471 mg, 92%) which crystallised from CH_2Cl_2/petrol, m p. 89-90°, $[\alpha]_D$
54, $CHCl_3$)

*no)ethyl (*E*)-(4a*S*,10*S*,10a*S*)-10-Hydroxy-7-methoxy-3,4,4a,9,10,10a-hexahydrophenanthren-*
cetate (+)-(**10**) The (4a*S*, 10*S*, 10a*S*) ester (+)-(**4**) (180 mg, 0.57 mmol) was converted to the
ethyl ester by a method similar to that described for the preparation of the (*E*) racemic analogue
on by radial chromatography (10% MeOH/$CHCl_3$) gave the *ester* (+)-(**10**) (130 mg, 64% over
solid, m p 88-90°, $[\alpha]_D$ = +20 4° (c = 0 51, $CHCl_3$)

*no)ethyl (*E*)-(4a*R*,10*R*,10a*R*)-10-Hydroxy-7-methoxy-3,4,4a,9,10,10a-hexahydrophenanthren-*
cetate (-)-(**10**) The (4a*R*,10*R*,10a*R*) ester (-)-(**4**) (400 mg, 1.27 mmol) was converted to the
ethyl ester by a method similar to that described for the preparation of the (*E*) racemic analogue
on by radial chromatography (10% MeOH/$CHCl_3$) gave the *ester* (-)-(**4**) (340mg, 75% over two
d, m p 89-91°, $[\alpha]_D$ = -18 9° (c = 0 56, $CHCl_3$)

*tion of Ethyl (*E*)-(1*R**,4aS*,10S*,10aS*)-1-Ethyl-10-hydroxy-7-methoxy-3,4,4a,9,10,10a-hexa-*
*ren-2(1*H*)-ylideneacetate* (**8**) The alcohol (**8**) (1 10 g, 3 2 mmol) was esterified with (*R*)-(-)-*O*-
acid (630 mg, 3 8 mmol) using oxalyl chloride/DMF according to the procedure described for the
the camphanate (**18**). Radial chromatography (10% EtOAc/petrol) separated the mixture of
ric *O*-methylmandelates The higher R_f isomer, the *(1*R*,4aS,10S,10aS)-O-methylmandelate* (**20**)
, was obtained as a gum, which by h p l c. analysis (5% EtOAc/petrol, 5 0 ml min^{-1}, R_t 7 2 min)
d e , $[\alpha]_D$ = -33 0° (c = 1 31, $CHCl_3$), Found. C, 73 24; H, 7 48% $C_{30}H_{36}O_6$ requires C,
%; ^{1}H n m r (300 MHz, $CDCl_3$). δ 0 56 (dd, *J* 7 5, 7 5 Hz, 3H, $C(H)HC\underline{H}_3$), 1 26 (ddq, *J*
, 1H, $C(\underline{H})HCH_3$), 1.30 (apparent t, *J* 7 Hz, 3H, $OCH_2C\underline{H}_3$), 1.32 (dddd, *J* 4, 13, 13, 13 Hz,
45 (ddq, *J* 11 5, 13, 7 5 Hz, 1H, $C(H)\underline{H}CH_3$), 1 96 (ddd, *J* 4, 11, 11 Hz, 1H, H-10a), 2 05
, 13, 13 Hz, 1H, H-3_{ax}), 2 30 (ddd, *J* 3 5, 4, 11.5 Hz, 1H, H-1), 2 55 (m, $W_{h/2}$ 24 Hz, 1H, H-
J 10, 16 Hz, 1H, H-9_{ax}), 2 91 (ddd, *J* 3, 11, 13 Hz, 1H, H-4a), 3 07 (dd, *J* 5, 16 Hz, 1H, H-
H, C2'-OMe), 3 73 (s, 3H, OMe), 3.92 (dm, *J* 13 Hz/$W_{h/2}$ 8 Hz, 1H, H-3_{eq}), 4 11-4 21 (m,
3), 4 82 (s, 1H, H-2'), 5 20 (ddd, *J* 5, 10, 11 Hz, 1H, H-10), 5 66 (d, *J* 1.5 Hz, 1H, vinyl-H),
Hz, 1H, H-8), 6 72 (dd, *J* 2.5, 8 5 Hz, 1H, H-6), 7.15 (d, *J* 8.5 Hz, 1H, H-5), 7 34-7 50 (m,
C n.m r (75 5 MHz, $CDCl_3$) δ 11.7 ($CH_2\underline{C}H_3$), 14 3 ($OCH_2\underline{C}H_3$), 18 6 ($\underline{C}H_2CH_3$), 24 3 (C-
), 35 4 (C-4a), 35 9 (C-9), 47 3 (C-1), 48.7 (C-10a), 55 2 (OMe), 57.4 (2'-OMe), 59 6
70 9 (C-10), 82 9 (C-2'), 112 7 (C-6), 113 4 (C-8), 115 6 ($\underline{C}HCO_2Et$), 126 8 (C-2", C-6"),
28 7 (C-3", C-5"), 128 8 (C-4"), 130 3 (C-4b), 134 3 (C-1"), 136.1 (C-8a), 157 9 (C-7),
56.5 ($\underline{C}O_2Et$), 170 3 (C-1'), *m/z*. 326 (25), 283 (6), 253 (6), 172 (14), 171 (62), 147 (7), 122

*4a*R*,10*R*,10a*R*)-O-methylmandelate* (**21**) (716 mg, 46%), which by h.p l c analysis (R_t 9 5
0% d e , crystallised from CH_2Cl_2/petrol, m.p 86-7°, $[\alpha]_D$ = -13 7° (c = 1 11, $CHCl_3$), Found
36% $C_{30}H_{36}O_6$ requires C, 73 15, H, 7 37%, ^{1}H n m r (300 MHz, $CDCl_3$) δ 0 24 (dd, *J*
H, $C(H)HC\underline{H}_3$), 0 93 (ddq, *J* 3 5, 13, 7 5 Hz, 1H, $C(\underline{H})HCH_3$), 1 26 (dddd, *J* 4, 13, 13, 13
), 1 30 (apparent t, *J* 7 Hz, 3H, $OCH_2C\underline{H}_3$), 1 31 (ddq, *J* 11 5, 13, 7.5 Hz, 1H, $C(H)\underline{H}CH_3$),
5, 4, 11.5 Hz, 1H, H-1), 1.85 (ddd, *J* 4, 11, 11 Hz, 1H, H-10a), 1 95 (dddd, *J* 1 5, 5, 13, 13
), 2 51 (m, $W_{h/2}$ 24 Hz, 1H, H-4_{eq}), 2 80 (dd, *J* 10, 16 Hz, 1H, H-9_{ax}), 2 87 (ddd, *J* 3, 11, 13
, 3 26 (dd, *J* 5, 16 Hz, 1H, H-9_{eq}), 3 43 (s, 3H, C2'-OMe), 3 75 (s, 3H, OMe), 3.83 (dm, *J* 13
1H, H-3_{eq}), 4 07-4 23 (m, 2H, $OC\underline{H}_2CH_3$), 4 78 (s, 1H, H-2'), 5 13 (ddd, *J* 5, 10, 11 Hz, 1H,
, *J* 1 5 Hz, 1H, vinyl-H), 6 55 (d, *J* 2 5 Hz, 1H, H-8), 6 72 (dd, *J* 2 5, 8 5 Hz, 1H, H-6), 7 14
H, H-5), 7.36-7 50 (m, 5H, ArH"), ^{13}C n m r (75 5 MHz, $CDCl_3$) δ 11.1 ($CH_2\underline{C}H_3$), 14 3
18 2 ($\underline{C}H_2CH_3$), 24 2 (C-3), 32.7 (C-4), 35 3 (C-4a), 36 5 (C-9), 46 7 (C-1), 48 8 (C-10a),
7 2 (2'-OMe), 59 6 ($O\underline{C}H_2CH_3$), 70 6 (C-10), 82 4 (C-2'), 112 7 (C-6), 113.5 (C-8), 115 3
27 0 (C-5), 127 3 (C-2", C-6"), 128 8 (C-3", C-5"), 129 0 (C-4"), 130 2 (C-4b), 134 3 (C-

1''), 136 4 (C-8a), 157 9 (C-7), 162 6 (C-2), 166 5 ($\underline{C}O_2Et$), 170.0 (C-1'); *m/z*: 327 (5), 326 (21), 283 (5), 253 (5), 172 (13), 171 (56), 122 (8), 121 (100)

*Ethyl (*E*)-(1*R*,4aS,10S,10aS)-1-Ethyl-10-hydroxy-7-methoxy-3,4,4a,9,10,10a-hexahydrophenanthren-2(1*H*)-ylideneacetate* (+)-(**8**) The (1*R*,4a*S*,10*S*,10a*S*)-*O*-methylmandelate (**20**) (730 mg, 1.48 mmol) was converted to the alcohol (+)-(**8**) by a method similar to that described for the preparation of (-)-(**4**) Purification by radial chromatography (30% EtOAc/petrol) gave the *alcohol* (+)-(**8**) (443 mg, 87%) which crystallised from CH_2Cl_2/petrol, m.p. 132-3°, $[\alpha]_D$ = +2 5° (c = 1 04, $CHCl_3$).

*Ethyl (*E*)-(1S,4a*R*,10*R*,10a*R*)-1-Ethyl-10-hydroxy-7-methoxy-3,4,4a,9,10,10a-hexahydrophenanthren-2(1*H*)-ylideneacetate* (-)-(**8**) The (1*S*,4a*R*,10*R*,10a*R*)-*O*-methylmandelate (**21**) (715 mg, 1 45 mmol) was converted to the alcohol (-)-(**8**) by a method similar to that described for the preparation of (-)-(**4**). Purification by radial chromatography (30% EtOAc/petrol) gave the *alcohol* (-)-(**8**) (400 mg, 80%) which crystallised from CH_2Cl_2/petrol, m p 132-3°, $[\alpha]_D$ = -2 7° (c = 1 13, $CHCl_3$)

*2-(Dimethylamino)ethyl (*E*)-(1*R*,4aS,10S,10aS)-1-Ethyl-10-hydroxy-7-methoxy-3,4,4a,9,10,10a-hexahydrophenanthren-2(1*H*)-ylideneacetate* (+)-(**14**). The (1*R*,4a*S*,10*S*,10a*R*) ester (+)-(**8**) (400 mg, 1.16 mmol) was converted to the dimethylaminoethyl ester (+)-(**14**) by a method similar to that described for the preparation of the analogue (**10**) Purification by radial chromatography (10% MeOH/$CHCl_3$) gave the *ester* (+)-(**14**) (412 mg, 92% over two steps) as a solid, m p 135-7°, $[\alpha]_D$ = +6 6° (c = 1 22, $CHCl_3$)

*2-(Dimethylamino)ethyl (*E*)-(1S,4a*R*,10*R*,10a*R*)-1-Ethyl-10-hydroxy-7-methoxy-3,4,4a,9,10,10a-hexahydrophenanthren-2(1*H*)-ylideneacetate* (-)-(**14**) The (1*S*,4a*R*,10*R*,10a*S*) ester (-)-(**8**) (400 mg, 1 16 mmol) was converted to the dimethylaminoethyl ester (-)-(**14**) by a method similar to that described for the preparation of the analogue (**10**) Purification by radial chromatography (10% MeOH/$CHCl_3$) gave the *ester* (-)-(**14**) (368 mg, 82% over two steps) as a solid, m p 135-7°, $[\alpha]_D$ = -6 3° (c = 1 21, $CHCl_3$)

Determination of Na^+,K^+-ATPase Inhibitory Activity

Na^+,K^+-ATPase activity was determined using pyruvate kinase and lactate dehydrogenase in a coupled enzyme assay [31] The assay medium consisted of 100 m*M* NaCl, 10 m*M* KCl, 3 m*M* $MgCl_2$, 0.1 m*M* EDTA, 50 m*M* imidazole (pH 7 5 at 30°C), 3 m*M* ATP, 4 5 m*M* phosphoenolpyruvate, 0 5 m*M* NADH, 2 5 U ml^{-1} of pyruvate kinase, 2 5 U ml^{-1} of lactate dehydrogenase and 0 01 U ml^{-1} of ATPase in a total volume of 3 ml The ATPase activity was measured at ambient temperature (30-35°C) by the decrease in absorption at 340 nm, using a Varian DMS-80 UV-Visible Spectrophotometer, in quartz cells with path length 1 cm.

Mono(cyclohexylammonium) phosphoenolpyruvate, disodium ATP, NADH and Na^+,K^+-ATPase were obtained from Sigma Chemical Co , USA Pyruvate kinase and lactate dehydrogenase were obtained from Boehringer Mannheim, Australia. All other chemicals were of analytical grade The Na^+,K^+-ATPase (product number A 7510) was the sodium iodide extracted fraction of Nakao *et al* [32] from porcine cerebral cortex and had a total activity of between 0 45-0 51 U mg^{-1} protein, depending on the batch, of which 3-6% was ouabain insensitive

Analogues (as their free bases) were introduced as dimethylsulphoxide solutions so that the concentration of the solvent was always 1% (v/v) Suitable controls established that the amount of dimethylsulphoxide added did not influence the assays, and that the analogues had no influence on the activities of pyruvate kinase or lactate dehydrogenase The inhibitory activity of an analogue was usually determined by testing, in duplicate, four concentrations covering a 10-fold concentration range around the IC_{50} value. For all analogues, at all concentrations covered, equilibrium inhibition was established immediately and preincubation was unnecessary The IC_{50} value was determined by interpolation (with the exception of analogues with $IC_{50} > 1$ m*M*, which were determined by extrapolation) of a Hill plot of the form

$$\log \frac{\gamma}{100 - \gamma} = h \log [C] - \log IC_{50}$$

where γ is the percentage inhibition of ouabain sensitive activity at an analogue concentration [C].[11] For all analogues linear plots were obtained and the Hill coefficient *h* was equal to 1.0 ± 0 1

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