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Synthetic Studies Towards Paspalicine: Preliminary Investigations, and the Synthesis of 3',4',7',7'a,9',10',11',11'a-Octahydro-4',4',7'a-trimethylspiro[1,3-dioxolane]-2,8'(6'*H*)-2'*H*-3',5'a-epoxynaphth [2,1-*b*]oxepin-2'-one

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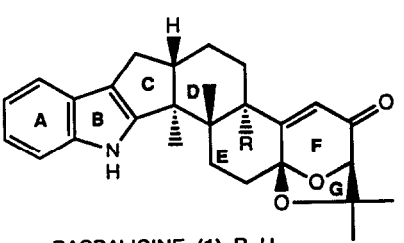
Keywords: Indole-diterpene mould metabolites; paspalicine; β-pyrone formation, ketalisation, X-ray crystal structure determination.

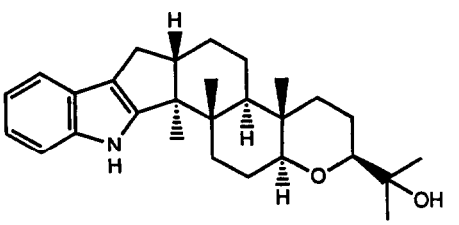
Abstract: Preliminary investigations directed towards the synthesis of the indole-diterpene mould metabolite, paspalicine **1**, are described. Following the preparation of the β-pyrone ketal **7**, which contains the characteristic functional group of paspalicine, the compound **25**, which constitutes rings D-G of paspalicine with the correct relative stereochemistry, has been synthesised in eight steps from the monoketal **12** of the Wieland-Miescher ketone, in an overall yield of 8%.

Paspalicine (**1**) and paspalinine (**2**) are two of the simpler members of a group of mould metabolites derived from tryptophan and a C-19 component of presumed diterpenoid origin. Paspalicine was first isolated by a Swiss group in the mid-1960's and paspalinine somewhat later, by Clardy *et al*[2], from the mycelium of *Claviceps paspali* Stevens et Hall. The structures of both paspalicine[3] and paspalinine[2] were established by X-ray crystallography. Aside from their intrinsic chemical interest these metabolites, and particularly those which, like paspalinine, contain an angular hydroxy-group at position 4b, are of considerable importance, owing to their potent tremorgenic properties. Indeed, paspalinine (**2**) appears to be responsible, at least in part, for the neurological disorder known as 'paspalum staggers', an affliction suffered by livestock that has grazed on *Paspalum dilatatum* pastures infected with the fungus, *Claviceps paspali*.[4] Clinical signs of paspalum staggers, which have occurred occasionally in the Southern United States, are sustained tremors and convulsions, which in severe cases can prove fatal.

The first total synthesis of paspalicine and paspalinine has been reported very recently by Smith *et al*.[5] In this communication we report an independent approach to the unusual β-pyrone ketal functionality[6] of paspalicine, which we believe offers an efficient alternative to the elegant route developed by Smith *et al.*



PASPALICINE (**1**) R=H
PASPALININE (**2**) R=OH

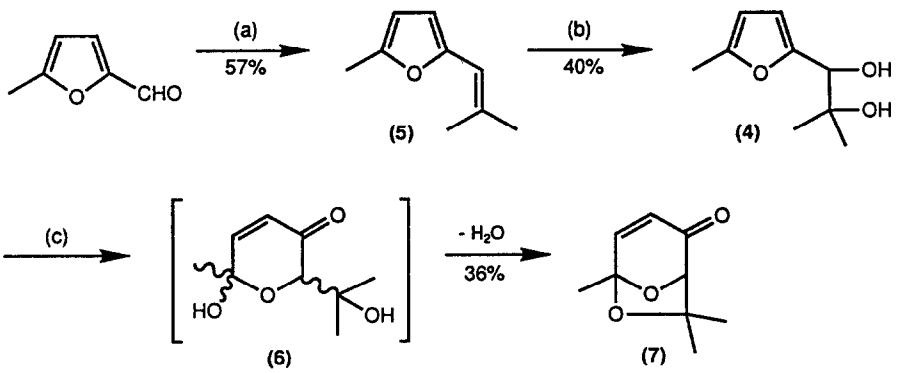


PASPALINE (**3**)

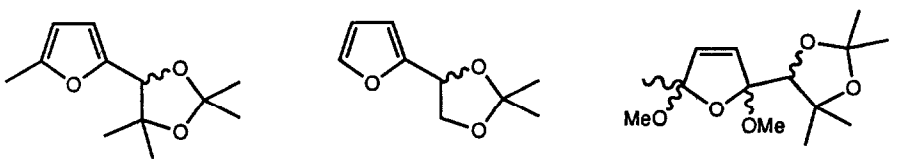
In exploring synthetic routes to paspalicine we recognised at the outset that the most challenging problems involved the construction of the transoid hydrindane system which comprises rings C and D, and the β-pyrone ketal grouping, which comprises rings F and G. Whereas, at the inception of our work, the problems attending the construction of rings C and D, and the attachment of the indole ring, had in principle been solved by Smith *et al* in their first synthesis of paspaline (3)[7] (and an alternative synthesis has subsequently been reported[8]) there was no record of the preparation of the β-pyrone ketal system which constitutes rings E-G, and it was therefore to the synthesis of this part of the molecule that we initially focussed our attention.

Compounds containing the 6-hydroxy-β-pyrone grouping can conveniently be prepared by the oxidative ring expansion of a 2-hydroxymethylfuran derivative.[9,10] If an additional, fortuitously placed, hydroxy-group is present in the product, cyclisation may well be possible to give the desired ketal function. Reduced to its simplest terms in a model system, this requires the preparation of the diol **4**, which should readily be obtainable from 5-methylfurfural *via* the isopropylidene derivative **5**. Oxidative ring enlargement of **4** should then give the diol **6**, from which the desired model β-pyrone ketal **7** should be obtainable by acid-catalysed cyclisation (Scheme 1). In the event this sequence of reactions was readily accomplished by Wittig reaction of 5-methylfurfural with isopropylidenetriphenylphosphorane, followed by hydroxylation of the 2-(2′-methylpropenyl)-5-methylfuran **5** so obtained to the corresponding diol **4** by means of osmium tetroxide-N-methylmorpholine N-oxide (NMO).

Scheme 1



Reagents :-
(a) $Ph_3P{=}CMe_2$ (b) OsO_4, NMO (c) mcpba

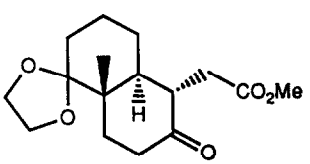


(8) (9) (10)

Our first attempt to carry out the oxidative ring expansion of the diol **4** was performed on the acetal **8**, since an exactly analogous reaction had earlier been reported on the related acetal **9** by Achmatowicz and co-workers.[10] This involves the bromination of the acetal **9** in anhydrous methanol at -25°C, followed by acid hydrolysis. In our hands bromination of the acetal in methanol gave the corresponding 2,5-dimethoxy-2,5-dihydro derivative **10** as a mixture of diastereoisomers, but we failed to obtain any trace of the diol **6** following acid hydrolysis. Accordingly, we resorted to direct oxidation of the diol **4** by means of m-chloroperbenzoic acid, and were gratified to find that the β-pyrone diol **6**, initially obtained, cyclised spontaneously under the reaction conditions, with formation of the desired ketal, 3,7-epoxy-2,2,7-trimethyl-4-oxo-2,3,4,7-tetrahydro-oxepin (**7**).

In applying this approach to the synthesis of paspalicine we clearly had to make provision for the introduction of the five-membered ring C and the indole ring, and we therefore selected as our initial synthetic target the naphthofuran derivative **11**, which we hoped to prepare from the monoketal **12**[11] of the Wieland-Miescher ketone.

The first attempt to prepare the furan derivative **11** involved the reductive alkylation of the monoketal **12** with lithium and liquid ammonia, followed by methyl bromoacetate, with the intention of preparing the furan **11** by reduction of the enol-lactone derived from the keto-ester **13** so obtained. However, the maximum yield (30%) of keto-ester **13** obtained did not justify the pursuit of this approach, and we therefore examined what is essentially a variant of this route, namely, Warren and Brownbridge's butenolide synthesis,[12] which involves alkylation of the enolate ion of the α-phenylthioketone **14** with sodium iodoacetate, followed by reduction, lactonisation, elimination, and further reduction. However, formation of the phenylthioketone **14** was achieved in only very modest yield, and the subsequent alkylation gave a complex mixture of products which appeared to contain only 25-30% yield of the required keto-ester; hence this route was not further pursued. Similarly, an attempt to apply the carbenoid approach[13] to the synthesis of a substituted furoic ester also foundered when it was found impossible to obtain a sufficiently high yield of the hydroxymethylene ketone **15**. These approaches to the furan derivative **11** proved to be impracticable because the reductive alkylation/acylation of the enone **12** proceeded in unacceptably low yield, and it was clear that only the most reactive alkylating reagents were likely to give high yields in this reaction. In order to test this hypothesis, the ketal enone **12** was reductively alkylated with lithium, liquid ammonia and allyl bromide, from which the allylketone **16** was obtained in 85% yield.



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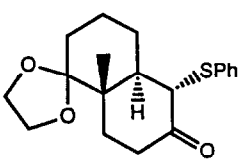

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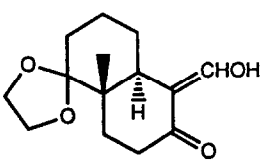
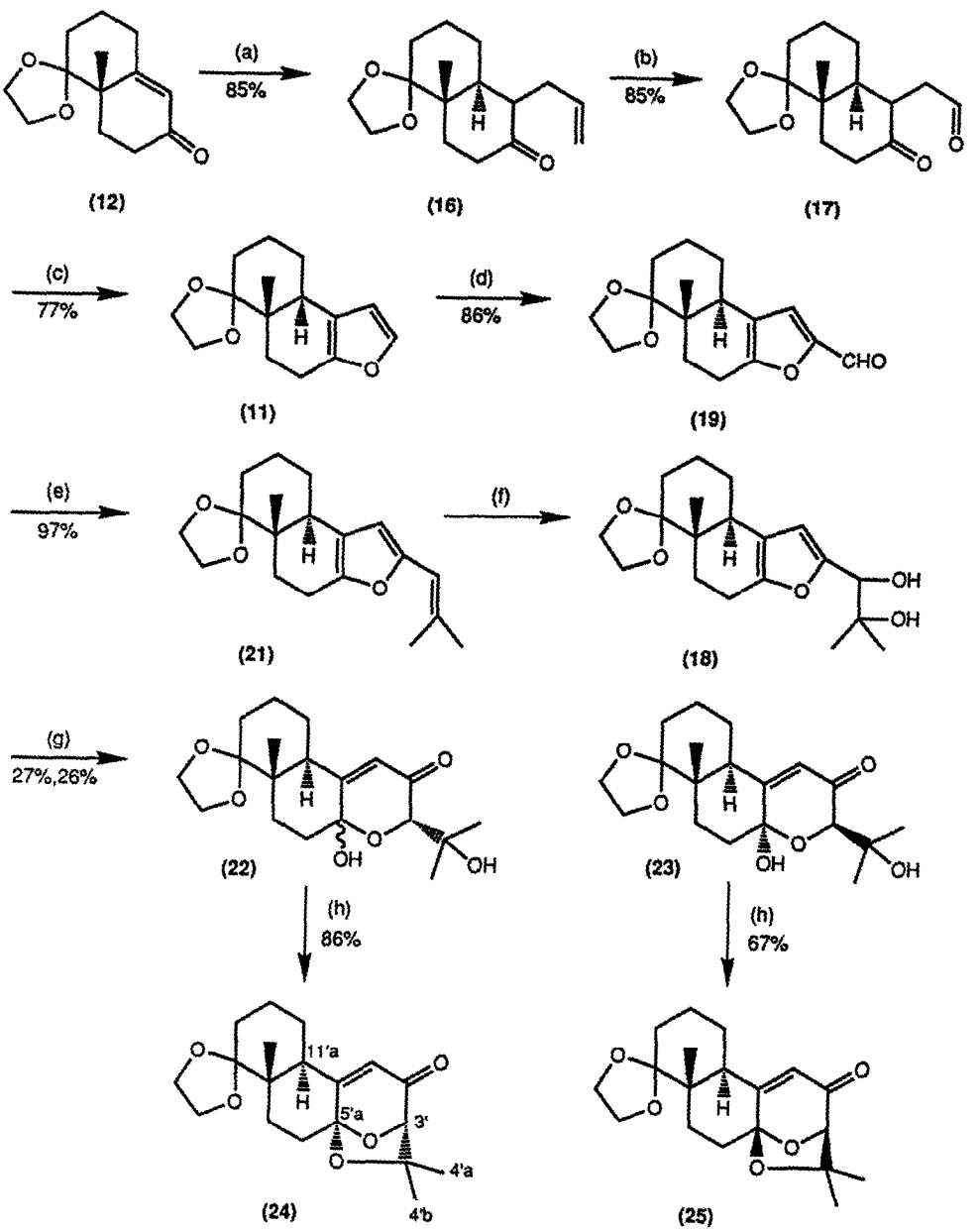


(15)

The isolation of the ketone **16** afforded us an opportunity to prepare the naphthofuran derivative **11** by one of the oldest known routes to furans. Ozonolysis of **16** gave the ketoaldehyde **17** (85%), which was then efficiently cyclised to the desired furan **11** by means of acetic anhydride (Scheme 2). With the naphthofuran **11** in hand, the subsequent stages to the critical substrate **18** required for the oxidative ring expansion were

Scheme 2

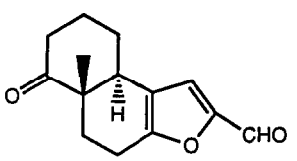


Reagents :-
(a) 1. Li , NH_3 2. allyl bromide (b) 1. O_3 , dcm 2. PPh_3 (c) Ac_2O , AcOH , reflux (d) DMF , $POCl_3$
(e) $(CH_3)_2C{=}PPh_3$ (f) OsO_4 , NMO (g) mcpba (h) $CuSO_4$, benzene , tosic acid

achieved in unexceptional fashion. Vilsmeier-Haack formylation of **11** gave the aldehyde **19** in 86% yield when acidic work-up conditions were avoided; otherwise, some ketoaldehyde **20** was obtained, together with a diminished yield (37%) of ketal aldehyde **19**.

Wittig condensation of **19** with isopropylidene triphenylphosphorane gave the isobutenylfuran derivative **21**, which was then oxidised by means of osmium tetroxide and N-methylmorpholine N-oxide to a mixture of the diastereoisomeric diols **18** (74%). Interestingly, during the chromatographic purification of **18** a small amount (9%) of diol A **22**, obtained by the oxidative ring expansion of **18**, was also isolated. The secure identification of this diol (**22**) followed the first oxidative ring expansion of the pure diols **18**, which was achieved by means of m-chloroperbenzoic acid. The chromatographically purified product consisted of diol A (**22**), m.p. 178-182°C (57%), and diol B (**23**), m.p. 144-145°C (36%), whose stereochemistries at this stage were unknown. Subsequently, these diols were prepared in improved yield in a combined process from the isobutenylfuran **21** in which the hydroxylation product **18** was partially purified by flash chromatography, then immediately oxidised by m-chloroperbenzoic acid.

Following the isolation of diol A, which was the first of the diols to be crystallised and purified, the course of its cyclisation by means of anhydrous copper sulphate was examined. The product, obtained in 86% yield, clearly had the required gross β-pyrone ketal structure (**24** or **25**) (i.r., proton and ^{13}C spectra), and only the stereochemistry at positions 3′ and 5′a remained to be determined. This was deduced from the observation of a very small (0.7%) nuclear Overhauser enhancement of the signal owing to the proton at position 11′a when the protons of methyl group 4′b (δ 1.15 ppm), attached to position 4′, were irradiated. This n.O.e. was reproducible, and would be expected to be very small in view of the relatively large intermolecular distance (≈ 3.5Å) between the relevant protons. We therefore considered this effect to be significant, and tentatively deduced that this ketal has the stereochemistry shown in **24**, i.e. it had the undesired stereochemistry in which the proton at position 11′a is *cis* with respect to the isopropoxy bridge. Its progenitor, diol A, presumably has the stereochemistry depicted in **22**.



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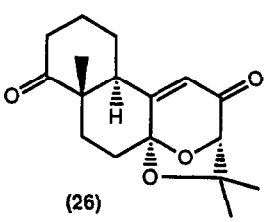

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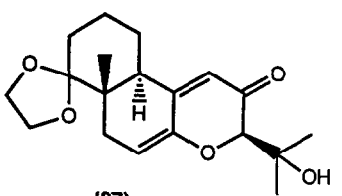

(27)

In another preparation a reduced yield (74%) of **24** was obtained, and a small amount (5%) of a by-product was isolated by hplc, which proved to be the corresponding ketone, presumably with the stereochemistry shown in **26**.

The stereochemistry of the diols A and B is obviously of vital importance in determining the stereochemistry of the cyclisation product (**24** or **25**), provided that the cyclisation conditions are sufficiently mild to ensure that epimerisation at C-3′ does not occur. At this stage we succeeded in obtaining a single crystal of diol B suitable for X-ray crystal structure determination, which revealed that diol B has the structure and stereochemistry shown in **23**. A drawing of the structure of the molecule is shown in Figure 1, interatomic distances and bond angles are given in Tables 1 and 2, and crystallographic data in Table 3

Table 1. Interatomic distances (pm) for (**23**) with estimated standard deviations (e.s.d.'s) in parentheses.

C(5)-O(1)	142.2(3)	C(7')-O(1)	142.9(3)
C(4)-O(3)	142.2(3)	C(7')-O(3)	142.2(3)
C(5)-C(4)	149.0(3)	H(4/1)-C(4)	93.8(20)
H(4/2)-C(4)	98.6(19)	H(5/1)-C(5)	94.7(19)
H(5/2)-C(5)	97.8(21)	C(2')-C(1')	145.1(3)
C(10'b)-C(1')	133.2(3)	H(1')-C(1')	95.9(16)
C(3')-C(2')	151.1(4)	O(17')-C(2')	123.0(3)
O(4')-C(3')	141.7(3)	C(11')-C(3')	154.3(4)
H(3')-C(3')	99.3(16)	C(4'a)-O(4')	141.9(2)
C(5')-C(4'a)	151.8(4)	C(10'b)-C(4'a)	151.6(4)
O(15')-C(4'a)	140.7(3)	C(6')-C(5')	152.7(4)
H(5'/1)-C(5')	98.7(17)	H(5'/2)-C(5')	100.9(16)
C(6'a)-C(6')	152.8(4)	H(6'/1)-C(6')	100.1(16)
H(6'/2)-C(6')	97.6(16)	C(7')-C(6'a)	154.9(4)
C(10'a)-C(6'a)	155.7(4)	C(14')-C(6'a)	153.2(4)
C(8')-C(7')	151.8(4)	C(9')-C(8')	152.0(4)
H(8'/1)-C(8')	98.4(16)	H(8'/2)-C(8')	99.8(18)
C(10')-C(9')	152.6(4)	H(9'/1)-C(9')	98.3(18)
H(9'/2)-C(9')	98.6(16)	C(10'a)-C(10')	151.8(4)
H(10'1)-C(10')	98.1(16)	H(10'/2)-C(10')	99.6(17)
C(10'b)-C(10'a)	151.1(4)	H(10'a)-C(10'a)	94.6(15)
C(12')-C(11')	151.0(4)	C(13')-C(11')	150.9(4)
O(16')-C(11')	143.2(3)	H(12'/1)-C(12')	101.3(22)
H(12'/2)-C(12')	98.8(20)	H(12'/3)-C(12')	96.6(21)
H(13'/1)-C(13')	102.4(22)	H(13'/2)-C(13')	102.8(23)
H(13'/3)-C(13')	97.5(21)	H(14'/1)-C(14')	99.1(22)
H(14'/2)-C(14')	98.8(18)	H(14'/3)-C(14')	95.1(19)
H(15')-O(15')	90.9(22)	H(16')-O(16')	89.0(26)

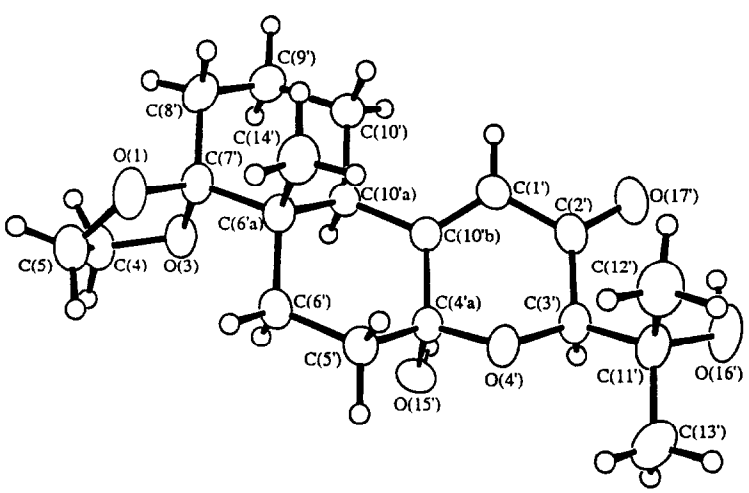

Figure 1.

Table 2. Angles (°) between interatomic vectors for **(23)** with e.s.d.'s in parentheses

C(7')-O(1)-C(5)	108.4(2)	C(7')-O(3)-C(4)	106.5(2)
C(5)-C(4)-O(3)	102.8(2)	H(4/1)-C(4)-O(3)	107.6(12)
H(4/1)-C(4)-C(5)	113.0(12)	H(4/2)-C(4)-O(3)	109.8(11)
H(4/2)-C(4)-C(5)	110.6(11)	H(4/2)-C(4)-H(4/1)	112.5(15)
C(4)-C(5)-O(1)	104.5(2)	H(5/1)-C(5)-O(1)	108.3(11)
H(5/1)-C(5)-C(4)	115.3(11)	H(5/2)-C(5)-O(1)	110.7(12)
H(5/2)-C(5)-C(4)	111.3(12)	H(5/2)-C(5)-H(5/1)	106.8(16)
C(10'b)-C(1')-C(2')	121.1(2)	H(1')-C(1')-C(2')	115.7(9)
H(1')-C(1')-C(10'b)	122.7(9)	C(3')-C(2')-C(1')	117.9(2)
O(17')-C(2')-C(1')	121.5(2)	O(17')-C(2')-C(3')	120.4(2)
O(4')-C(3')-C(2')	111.1(2)	C(11')-C(3')-C(2')	113.6(2)
C(11')-C(3')-O(4')	107.1(2)	H(3')-C(3')-C(2')	104.9(9)
H(3')-C(3')-O(4')	111.3(9)	H(3')-C(3')-C(11')	108.9(9)
C(4'a)-O(4')-C(3')	116.7(2)	C(5')-C(4'a)-O(4')	103.4(2)
C(10'b)-C(4'a)-O(4')	111.2(2)	C(10'b)-C(4'a)-C(5')	112.0(2)
O(15')-C(4'a)-O(4')	110.8(2)	O(15')-C(4'a)-C(5')	108.4(2)
O(15')-C(4'a)-C(10'b)	110.8(2)	C(6')-C(5')-C(4'a)	113.0(2)
H(5'/1)-C(5')-C(4'a)	106.6(9)	H(5'/1)-C(5')-C(6')	110.1(9)
H(5'/2)-C(5')-C(4'a)	106.6(9)	H(5'/2)-C(5')-C(6')	112.2(9)
H(5'/2)-C(5')-H(5'/1)	108.1(13)	C(6'a)-C(6')-C(5')	112.3(2)
H(6'/1)-C(6')-C(5')	109.4(9)	H(6'/1)-C(6')-C(6'a)	110.6(10)
H(6'/2)-C(6')-C(5')	109.6(9)	H(6'/2)-C(6')-C(6'a)	109.1(10)
H(6'/2)-C(6')-H(6'/1)	105.7(13)	C(7')-C(6'a)-C(6')	110.4(2)
C(10'a)-C(6'a)-C(6')	108.4(2)	C(10'a)-C(6'a)-C(7')	107.3(2)
C(14')-C(6'a)-C(6')	110.0(2)	C(14')-C(6'a)-C(7')	109.5(2)
C(14')-C(6'a)-C(10'a)	111.2(2)	O(3)-C(7')-O(1)	106.2(2)
C(6'a)-C(7')-O(1)	109.8(2)	C(6'a)-C(7')-O(3)	108.4(2)
C(8')-C(7')-O(1)	109.7(2)	C(8')-C(7')-O(3)	109.8(2)
C(8')-C(7')-C(6'a)	112.7(2)	C(9')-C(8')-C(7')	111.2(2)
H(8'/1)-C(8')-C(7')	108.7(10)	H(8'/1)-C(8')-C(9')	109.1(9)
H(8'/2)-C(8')-C(7')	110.8(10)	H(8'/2)-C(8')-C(9')	109.2(10)
H(8'/2)-C(8')-H(8'/1)	107.8(13)	C(10')-C(9')-C(8')	112.1(2)
H(9'/1)-C(9')-C(8')	111.1(10)	H(9'/1)-C(9')-C(10')	109.7(10)
H(9'/2)-C(9')-C(8')	109.7(10)	H(9'/2)-C(9')-C(10')	109.0(9)
H(9'/2)-C(9')-H(9'/1)	104.9(14)	C(10'a)-C(10')-C(9')	111.4(2)
H(10'/1)-C(10')-C(9')	109.0(9)	H(10'/1)-C(10')-C(10'a)	110.3(9)
H(10'/2)-C(10')-C(9')	108.0(10)	H(10'/2)-C(10')-C(10'a)	110.5(10)
H(10'/2)-C(10')-H(10'/1)	107.6(13)	C(10')-C(10'a)-C(6'a)	112.9(2)
C(10'b)-C(10'a)-C(6'a)	111.1(2)	C(10'b)-C(10'a)-C(10')	113.7(2)
H(10'a)-C(10'a)-C(6'a)	105.1(9)	H(10'a)-C(10'a)-C(10')	107.3(9)
H(10'a)-C(10'a)-C(10'b)	106.0(9)	C(4'a)-C(10'b)-C(1')	119.9(2)
C(10'a)-C(10'b)-C(1')	124.2(2)	C(10'a)-C(10'b)-C(4'a)	115.9(2)
C(12')-C(11')-C(3')	111.1(2)	C(13')-C(11')-C(3')	110.0(2)
C(13')-C(11')-C(12')	111.6(3)	O(16')-C(11')-C(3')	108.0(2)
O(16')-C(11')-C(12')	110.1(2)	O(16')-C(11')-C(13')	105.7(2)
H(12'/1)-C(12')-C(11')	110.4(12)	H(12'/2)-C(12')-C(11')	112.1(12)
H(12'/2)-C(12')-H(12'/1)	106.2(17)	H(12'/3)-C(12')-C(11')	110.1(12)
H(12'/3)-C(12')-H(12'/1)	108.4(17)	H(12'/3)-C(12')-H(12'/2)	109.4(16)
H(13'/1)-C(13')-C(11')	111.9(13)	H(13'/2)-C(13')-C(11')	111.4(12)
H(13'/2)-C(13')-H(13'1)	109.4(17)	H(13'/3)-C(13')-C(11')	109.3(13)
H(13'/3)-C(13')-H(13'1)	106.9(17)	H(13'/3)-C(13')-H(13'/2)	107.7(17)
H(14'/1)-C(14')-C(6'a)	112.6(12)	H(14'/2)-C(14')-C(6'a)	111.8(11)
H(14'/2)-C(14')-H(14'/1)	105.2(15)	H(14'/3)-C(14')-C(6'a)	111.3(12)
H(14'/3)-C(14')-H(14'/1)	106.6(16)	H(14'/3)-C(14')-H(14'/2)	109.0(15)
H(15')-O(15')-C(4'a)	109.9(13)	H(16')-O(16')-C(11')	106.9(16)

Table 3. Crystallographic data for compounds (**23**) and (**25**)

	(**23**)	(**25**)
Crystal Data		
Formula	$C_{19}H_{28}O_6$	$C_{19}H_{26}O_5$
M	352.43	334.41
Crystal dimensions	0.7x0.4x0.2mm	0.8x0.45x0.2mm
System	Triclinic	Monoclinic
a /pm	666.9(1)	1117.6(1)
b /pm	1138.4(2)	931.4(1)
c /pm	1317.1(2)	1647.3(1)
α /°	66.48(1)	—
β /°	75.95(1)	102.11(1)
γ /°	80.77(1)	—
U /nm^{-3}	0.8871(3)	1.6766(3)
Space group	$P\bar{1}$	$P2_1/c$
Z	2	4
D_x / gcm^{-3}	1.32	1.32
$F(000)$	380.0	720
μ (Mo-K_α) /cm^{-1}	0.58	0.89
Data Collection		
Scan mode	$\omega/2\theta$	ω/θ
Scan width	2.0° + α-doublet splitting	1.6° + α-doublet splitting
Scan speeds / ° min^{-1}	2.0 - 29.3	1.5 - 8.0
$2\theta_{min,max}$ / °	4.0, 50.0	4.0, 50.0
No. of data collected	3427	3162
No. of data observed	2939[a]	2080[b]
Temp./ K	290	200
Refinement		
R[c]	0.0352	0.0473
R'[d]	0.0383	0.0575
weighting parameter g[e]	0.0002	0.0004
no. of parameters	338	227

Footnotes

a) Criterion for observed reflection, $|F_o| > 3.0\sigma(|F_o|)$

b) Criterion for observed reflection, $|F_o| > 4.0\sigma(|F_o|)$

c) $R = \Sigma(|F_o| - |F_c|) / \Sigma|F_o|$

d) $R' = \Sigma w(|F_o| - |F_c|)^2 / \Sigma w|F_o|^2$

e) $w = [\sigma^2(|F_o|) + g(|F_o|)^2]^{-1}$

The structure and stereochemistry of diol B having been thus definitively established, we confidently expected that, under mild conditions, it would cyclise to the desired β-pyrone ketal **25**, having the paspalicine stereochemistry, since it can only cyclise to the undesired isomeric ketal **24**[14], *via* the easily-generated oxonium ion, by prior epimerisation at C-3′, alpha to the carbonyl group. Indeed, treatment of diol B **23** with anhydrous copper sulphate and toluene p-sulphonic acid in benzene at room temperature gave the β-pyrone ketal **25** in 67% yield, together with a small amount (18%) of the diene **27**. Again, the structure and stereochemistry of **25** were established by a single crystal X-ray structure determination. A drawing of the structure of the molecule is shown in Figure 2, the interatomic distances and bond angles are given in Tables 4 and 5, and the crystallographic data in Table 3.

The stereochemistry of β-pyrone ketal **25** is thus established to be identical with that of rings D-G of paspalicine, an identity which receives confirmation from the ^{13}C n.m.r. spectra, since the chemical shifts observed for the ketal **25** are much closer to those of the corresponding carbon atoms in paspalicine (**1**) than are those of isomeric ketal **24** (Table 6).

Table 6 ^{13}C Chemical Shifts for ketals **24** and **25**, and the corresponding atoms in Paspalicine (**1**).

Carbon	Ketal **24**	Ketal **25**	Paspalicine (**1**)[4]
1′	120.68	119.99	118.4
2′	194.59	196.09	197.6
3′	86.91	88.22	88.4
4′	80.06	77.45	78.2
4′a	22.97	23.14	23.8
4′b	29.81	28.89	29.0
5′a	103.54	103.97	104.4
7′a	43.05	39.70	39.9
7′b	15.36	20.61	23.2
11′b	166.97	171.47	171.8

In summary, we have developed an efficient route to the characteristic β-pyrone ketal functionality of paspalicine, which has so far resulted in the preparation of the ketal **25**, with the requisite relative stereochemistry, in eight steps from the monoketal **12** of the Wieland-Miescher ketone, in an overall yield of 8.0%.

Experimental

M.p.s were determined on a Kofler hot-stage apparatus and are uncorrected. I.r. spectra were recorded on either Perkin-Elmer 1420 or a Philips PU 9706 spectrophotometer. N.m.r. spectra were recorded on either a Perkin-Elmer R32 instrument (^1H, 90MHz), a Jeol FX90Q F.T.(^1H 90 MHz and ^{13}C), a GE QE 300(^1H 300MHz and ^{13}C), or a Bruker W.H. 400 MHz spectrometer (^1H 400 MHz and ^{13}C). Solutions in deuteriochloroform, with tetramethylsilane as internal standard, were used, unless otherwise stated. Mass spectra were recorded on a Kratos MS25 instrument; accurate mass measurements were carried out using an A.E.I./Kratos MS 902/50 spectrometer.

All reactions in non-aqueous solution were carried out under nitrogen, unless otherwise stated.

Table 4. Interatomic distances (pm) for (**25**) with e.s.d.'s in parentheses.

C(5)-O(1)	142.8(4)	C(8')-O(1)	143.4(4)
C(4)-O(3)	143.0(4)	C(8')-O(3)	142.4(4)
C(5)-C(4)	149.6(6)	C(2')-C(1')	146.3(5)
C(11'b)-C(1')	134.9(4)	C(3')-C(2')	151.9(6)
O(13')-C(2')	121.6(4)	C(4')-C(3')	155.0(6)
O(12')-C(3')	143.7(4)	C(4'a)-C(4')	151.5(6)
C(4'b)-C(4')	151.3(6)	O(5')-C(4')	145.8(4)
C(5'a)-O(5')	143.9(4)	C(6')-C(5'a)	150.2(5)
C(11'b)-C(5'a)	153.1(5)	O(12')-C(5'a)	141.8(4)
C(7')-C(6')	153.2(6)	C(7'a)-C(7')	155.4(6)
C(7'b)-C(7'a)	153.2(5)	C(8')-C(7'a)	154.5(5)
C(11'a)-C(7'a)	156.1(5)	C(9')-C(8')	151.8(5)
C(10')-C(9')	153.2(5)	C(11')-C(10')	151.9(5)
C(11'a)-C(11'b)	149.5(4)	C(11')-C(11'a)	153.8(5)

All hydrogen atoms are in calculated positions with C-H = 96 pm

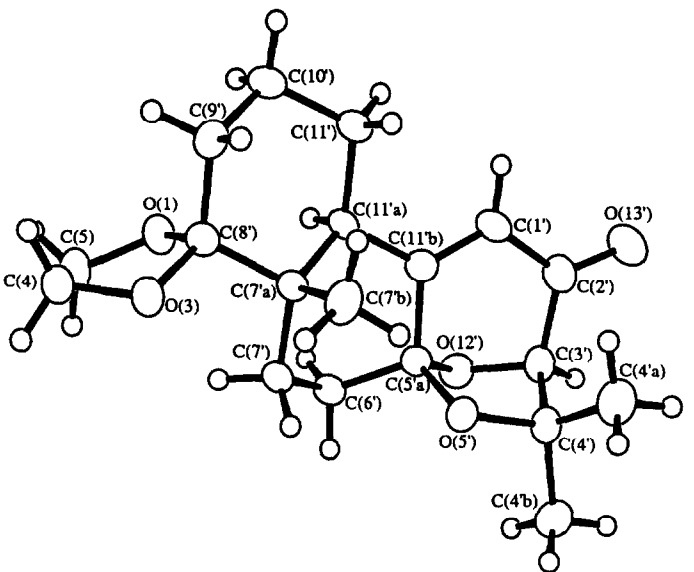

Figure 2.

Table 5. Angles (°) between interatomic vectors for (**25**) with e.s.d.'s in parentheses

C(8')-O(1)-C(5)	108.4(3)	C(8')-O(3)-C(4)	106.0(3)
H(4/1)-C(4)-O(3)	111.0(2)	H(4/2)-C(4)-O(3)	111.0(2)
H(4/2)-C(4)-H(4/1)	109.5(1)	C(5)-C(4)-O(3)	103.3(3)
C(5)-C(4)-H(4/1)	111.0(3)	C(5)-C(4)-H(4/2)	111.0(3)
C(4)-C(5)-O(1)	104.9(3)	H(5/1)-C(5)-O(1)	110.6(3)
H(5/1)-C(5)-C(4)	110.6(3)	H(5/2)-C(5)-O(1)	110.6(2)
H(5/2)-C(5)-C(4)	110.6(3)	C(2')-C(1')-H(1')	120.1(2)
C(11'b)-C(1')-H(1')	120.1(3)	C(11'b)-C(1')-C(2')	119.7(3)
C(3')-C(2')-C(1')	115.0(3)	O(13')-C(2')-C(1')	123.6(3)
O(13')-C(2')-C(3')	121.2(3)	H(3')-C(3')-C(2')	105.7(2)
C(4')-C(3')-C(2')	111.3(3)	C(4')-C(3')-H(3')	113.7(2)
O(12')-C(3')-C(2')	109.9(3)	O(12')-C(3')-H(3')	115.0(2)
O(12')-C(3')-C(4')	101.4(3)	C(4'a)-C(4')-C(3')	114.5(3)
C(4'b)-C(4')-C(3')	110.9(3)	C(4'b)-C(4')-C(4'a)	111.4(3)
O(5')-C(4')-C(3')	101.2(3)	O(5')-C(4')-C(4'a)	109.9(3)
O(5')-C(4')-C(4'b)	108.3(3)	H(4a'/1)-C(4'a)-C(4')	107.9(2)
H(4a'/2)-C(4'a)-C(4')	110.8(3)	H(4a'/3)-C(4'a)-C(4')	109.6(3)
H(4b'/1)-C(4'b)-C(4')	109.1(2)	H(4b'/2)-C(4'b)-C(4')	109.0(2)
H(4b'/3)-C(4'b)-C(4')	110.3(2)	C(5'a)-O(5')-C(4')	108.0(3)
C(6')-C(5'a)-O(5')	110.6(3)	C(11'b)-C(5'a)-O(5')	109.6(3)
C(11'b)-C(5'a)-C(6')	111.6(3)	O(12')-C(5'a)-O(5')	104.7(3)
O(12')-C(5'a)-C(6')	111.4(3)	O(12')-C(5'a)-C(11'b)	108.8(3)
H(6'/1)-C(6')-C(5'a)	109.0(2)	H(6'/2)-C(6')-C(5'a)	109.0(2)
C(7')-C(6')-C(5'a)	111.5(3)	C(7')-C(6')-H(6'/1)	108.9(2)
C(7')-C(6')-H(6'/2)	109.0(2)	H(7'/1)-C(7')-C(6')	107.9(2)
H(7'2)-C(7')-C(6')	107.8(2)	C(7'a)-C(7')-C(6')	115.8(3)
C(7'a)-C(7')-H(7'/1)	107.9(2)	C(7'a)-C(7')-H(7'/2)	107.9(2)
C(7'b)-C(7'a)-C(7')	109.1(3)	C(8')-C(7'a)-C(7')	110.1(3)
C(8')-C(7'a)-C(7'b)	109.4(3)	C(11'a)-C(7'a)-C(7')	109.8(3)
C(11'a)-C(7'a)-C(7'b)	110.9(3)	C(11'a)-C(7'a)-C(8')	107.4(3)
H(7b'/1)-C(7'b)-C(7'a)	111.8(2)	H(7b'/2)-C(7'b)-C(7'a)	107.4(2)
H(7b'/3)-C(7'b)-C(7'a)	109.2(2)	O(3)-C(8')-O(1)	106.1(3)
C(7'a)-C(8')-O(1)	109.0(3)	C(7'a)-C(8')-O(3)	108.9(3)
C(9')-C(8')-O(1)	108.4(3)	C(9')-C(8')-O(3)	110.9(3)
C(9')-C(8')-C(7'a)	113.2(3)	H(9'/1)-C(9')-C(8')	109.1(2)
H(9'/2)-C(9')-C(8')	109.1(2)	C(10')-C(9')-C(8')	110.9(3)
C(10')-C(9')-H(9'/1)	109.1(2)	C(10')-C(9')-H(9'/2)	109.1(2)
H(10'/1)-C(10')-C(9')	108.9(2)	H(10'/2)-C(10')-C(9')	108.9(2)
C(11')-C(10')-C(9')	111.6(3)	C(11')-C(10')-H(10'/1)	109.0(2)
C(11')-C(10')-H(10'/2)	108.9(2)	C(5'a)-C(11'b)-C(1')	117.1(3)
C(11'a)-C(11'b)-C(1')	126.5(3)	C(11'a)-C(11'b)-C(5'a)	116.4(3)
C(11'b)-C(11'a)-C(7'a)	111.9(3)	H(11'a)-C(11'a)-C(7'a)	107.1(2)
H(11'a)-C(11'a)-C(11'b)	105.4(2)	C(11')-C(11'a)-C(7'a)	113.1(3)
C(11')-C(11'a)-C(11'b)	114.6(3)	C(11')-C(11'a)-H(11'a)	103.9(2)
C(11'a)-C(11')-C(10')	111.5(3)	H(11'/1)-C(11')-C(10')	109.0(2)
H(11'/1)-C(11')-C(11'a)	108.9(2)	H(11'/2)-C(11')-C(10')	109.0(2)
H(11'/2)-C(11')-C(11'a)	109.0(2)	C(5'a)-O(12')-C(3')	101.7(3)

All hydrogen atoms are in calculated positions so that, where relevant, H-C-H = 109.5°

Crystal Structure Determination - All diffraction measurements for **23** were made at room temperature (290 K) on a Nicolet P3/F diffractometer, whilst those for **25** were made at 200 K on a Stoe STADI4 diffractometer. Both diffractometers used graphite monochromated Mo-K_α radiation (λ = 71.069 pm). The unit cell parameters of both compounds together with their estimated standard deviations were derived from a least-squares fit of the setting angles of 25 centred reflections in the range $20.0^0 < 2\theta < 25.0^0$. Details of data collection for both compounds are given in Table 3. Lorentz and polarisation corrections were applied to both data-sets together with a post structure-solution empirical absorption correction[15] to **23** and a semi-empirical absorption correction (using azimuthal psi scans) to **25**.

Both structures were solved by direct methods using SHELX 86,[16] and were refined by full-matrix least-squares using SHELX 76.[17] In both cases all non-hydrogen atoms were refined with anisotropic thermal parameters. For **23** all hydrogen atoms were located on Fourier difference syntheses and were freely refined with isotropic thermal parameters. The limited amount of data precluded this for **25** for which the hydrogen atoms were included in calculated positions (C-H = 96 pm). The weighting scheme $w = [\sigma^2(F_0)+g(F_0)^2]^{-1}$ was applied in both cases, where $\sigma(F_0)$ is derived from counting statistics and g a parameter adjusted during refinement so as to give a satisfactory analysis of variance.

Additional material available from the Cambridge Crystallographic Data Centre comprises non-hydrogen atomic co-ordinates, H atom co-ordinates and isotropic and anisotropic thermal parameters.

2-Methyl-5-(2-methylprop-1-enyl)furan(5). To a stirred suspension of isopropyltriphenylphosphonium iodide (4.79g, 11 mmol) in anhydrous ether (20 ml), cooled to 0°C, n-butyl lithium (1.6M; 6.8ml, 109mmol) was added dropwise. After the addition was complete, the reaction mixture was allowed to warm to room temperature and stirred for 2 hours, then recooled to 0°C. A solution of 5-methylfurfural (1.10 g, 10 mmol) in ether (10 ml) was added dropwise over a 10 minute period. The reaction mixture was stirred for 15 hours at room temperature, after which the precipitate which had formed was removed by filtration. The filtrate was diluted with ether (50 ml), washed with water (20 ml), and saturated aqueous sodium chloride solution (20 ml), and then dried ($MgSO_4$). Removal of the solvent under reduced pressure gave an oil which was purified by distillation (130°C, 20 mm Hg) to give *2-methyl-5-(2-methylprop-1-enyl)furan*(**5**) as a pale yellow oil (0.78 g, 57%); $\delta_H(CDCl_3$: 90 MHz) 1.85(3H, s), 1.95(3H, s), 2.30(3H, s), 5.95(1H, m), 6.00(1H, m), 6.05(1H, d, J 3Hz); m/z(%) 136(M^+, 2.7%), 126(5.8), 111(29.0), 97(27.4), 83(57.7), 69(11.7).

2-Methyl-5-(2-methyl-1,2-dihydroxypropyl)furan(4). A solution of 2-methyl-5-(2-methylprop-1-enyl)furan (1.0 g, 7.35 mmol) in a mixture of acetone (5 ml), water (5 ml) and t-butyl alcohol (1 ml), containing N-methylmorpholine N-oxide (950 mg, 8.1 mmol) and osmium tetroxide (8 mg, 0.03 mmol) was stirred at room temperature for 25 hours. A slurry composed of Florisil (1.5 g), sodium dithionite (0.15g), and water (10 ml) was added and the resulting mixture stirred for a further 30 minutes and then filtered through a pad of celite. The filter cake was washed with acetone (3 x 100 ml) and the filtrate neutralised to pH7 with dilute hydrochloric acid. The filtrate was concentrated under reduced pressure and the resulting residue was partitioned between ether (75 ml) and water (30 ml). The aqueous phase was separated and extracted with ether (2 x 40 ml). The combined ether extracts were washed with dilute hydrochloric acid (30 ml), water (30 ml) and saturated aqueous sodium chloride solution (30 ml), and dried ($MgSO_4$). Removal of the solvent under

reduced pressure gave an oil which was purified by chromatography on Kieselgel G (100 g) with dichloromethane-ether (85:15) as the eluent, to give the *diol* (**4**) (0.49g, 40%) as a colourless oil (Found: M^+, 170.09475. $C_9H_{14}O_3$ requires M, 170.094288); $\nu_{max}(CHCl_3)$: 3585, 3585-3200, 1560 cm^{-1}; $\delta_H(CDCl_3$:90MHz) 1.20(3H, s), 1.26(3H, s), 2.30(3H, s), 2.95-3.30(2H, br s, D_2O exchange), 4.45(1H, s), 5.90(1H, m), 6.25(1H, m); m/z(%), 170($\underline{M}^+$, 1.5%), 137(11.6), 112(83), 97(41), 91(8.3), 84(14.8), 69(4.9), 65(7.6).

Isopropylidene derivative of 2-methyl-5-(2-methyl-1,2-dihydroxypropyl)furan(8). A solution of the furan-diol (**4**) (400 mg, 2.35mmol) in freshly distilled 2,2-dimethoxypropane (5 ml) containing toluene-p-sulphonic acid (10 mg) was stirred under nitrogen for 1 hour. The solution was diluted with dichloromethane (40 ml) and washed with water (20 ml). The aqueous washing was extracted with dichloromethane (2 x 30 ml). The combined dichloromethane fractions were washed successively with saturated aqueous sodium bicarbonate solution (20 ml), water (20 ml) and saturated aqueous sodium chloride solution (30 ml), and then dried ($MgSO_4$). Removal of the solvent under reduced pressure gave a yellow oil which was purified by chromatography on Kieselgel G (20 g) with dichloromethane-hexane (3:7) as the eluent to give the *isopropylidene derivative* (**8**) (450 mg, 91%), as a colourless oil. (Found: M^+, 210.12606. $C_{12}H_{18}O_3$ requires M, 210.125586); $\nu_{max}(CHCl_3)$; 1565(s)cm^{-1}, $\delta_H(CDCl_3$: 90 MHz), 1.10(3H, s), 1.40(3H, s), 1.45(3H, s), 1.55(3H, s), 2.25(3H, d, J 2Hz), 4.75(1H, s), 5.9(1H, m), 6.25(1H, d, J 5Hz); m/z(%), 210($\underline{M}^+$, 1.9%), 195(6.6), 152(34.0), 137(5.1), 123(7.5), 111(11.1), 94(100), 79(26.8), 69(2.4).

3,7-Epoxy-2,2,7-trimethyl-4-oxo-2,3,4,7-tetrahydro-oxepin(7). A solution of the furan-diol (**4**) (196mg, 1.15 mmol) in anhydrous dichloromethane (4 ml) was added to a stirred solution of m-chloroperbenzoic acid (95%, 233 mg, 1.27 mmol) in dichloromethane (6 ml) at 0°C. The mixture was allowed to warm up to room temperature and stirred for 5 hours, after which it was filtered. The filtrate was diluted with dichloromethane (50 ml) and washed successively with 10% sodium sulphite solution (10 ml), saturated aqueous sodium bicarbonate solution (25 ml), water (15 ml), and saturated aqueous sodium chloride solution (15 ml), and then dried ($MgSO_4$). Removal of the solvent under reduced pressure gave a yellow solid residue which was purified by chromatography on Kieselgel G (70 g) with dichloromethane-hexane (50%) as the eluent, to afford 3,7-*epoxy*-2,2,7-*trimethyl*-4-*oxo*-2,3,4,7-*tetrahydro-oxepin*(**7**) (71mg, 36%) as a pale yellow solid, mp 53-57°C (with sublimation). (Found: M^+, 168.07855. $C_9H_{12}O_3$ requires M, 168.078635); $\nu_{max}(CHCl_3)$: 1690(s) cm, $\delta_H(CHCl_3$: 90 MHz), 1.20(3H, s), 1.45(3H, s), 1.70(3H, s), 4.30(1H, d, J 1.8Hz), 6.0(1H, dd, J 1.8, 9 Hz), 7.10(1H, d, J 9Hz); $\delta_c(CDCl_3$: 22.5 MHz) 22.69(q), 22.80(q), 29 00(q), 78.73(s), 88.54(d), 103.19(s), 126.27(d), 152.49(d), 194.69(s); m/z(%), 168(M^+, 3.7), 140(10.6), 110(33.3), 97(71.3), 82(43.1), 72(22.1)

3′,4′,4′a,5′,8′,8′a-Hexahydro-5′-methoxycarbonylmethyl-8′a-methylspiro[1,3-dioxolane-2,1′(2′*H*)-naphthalen]-6′(7′*H*)-one(13). A solution of the ketal-enone (**12**) (405 mg, 1.82 mmol) and water (50 mg, 2.7 mmol) in anhydrous THF (10 ml) was added dropwise to a stirred solution of lithium (38 mg, 5 48 mmol) in anhydrous liquid ammonia (70 ml) under an argon atmosphere. The solution was stirred for 1 hour, then a solution of methyl bromoacetate (4.20g, 27.5 mmol) in THF (4 ml) was added in one portion. Stirring was continued for another 30 minutes after which the ammonia was allowed to evaporate under a stream of argon. The resulting residue was partitioned between ether (3 x 30 ml) and water (20 ml). The combined ethereal extracts were washed with saturated aqueous sodium chloride solution (30 ml), and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave a yellow oily residue which was purified by chromatography on Kieselgel G (75 g) with chloroform as the eluent, to give the *ketoester*(**13**) (160 mg, 30%) as a pale yellow oil

(Found: C, 64.95; H, 8.3%; M^+, 296.16225. $C_{16}H_{24}O_5$ requires C, 64.8; H, 8.2%; M, 296.162362; $\nu_{max}(CHCl_3)$: 1730, 1710 cm^{-1}; δ_H ($CDCl_3$: 90 MHz), 1.28(3H, s), 1.2-2.1(9H, m), 2.1-3.0(5H, m), 3.7(3H, s), 3.8-4.0(4H, m); $\delta_c(CDCl_3$: 22.5MHz), 14.14(q), 22.64(t), 25.14(t), 29.9(t), 30.66(t), 31.58(t), 37.33(t), 42.64(s), 46.43(d), 47.46(d), 51.52(q), 65.01(t), 65.17(t), 112.36(s), 173.58(s), 210.20(s); m/z(%), 296(M^+, 3.9), 265(3.3), 209(5.0), 112(30.6), 99(76.7), 86(100), 79(76). 69(10.4).

3′,4′,4′a,5′,8′,8′a-Hexahydro-5′-phenylthio-8′a-methylspiro[1,3-dioxolane-2,1′(2′*H*)-naphthalen]-6′(7′*H*)-one(*14*). A solution of the ketal-enone (**12**) (470 mg, 2.11 mmol) and t-butyl alcohol (140 mg, 1.9 mmol) in dry ether (10 ml) was added dropwise to a stirred solution of lithium (32 mg, 4.65 mmol) in anhydrous liquid ammonia (50 ml) at -78°C, under an argon atmosphere. After 30 minutes at -78°C the coolant was removed and the reaction mixture allowed to reflux for an additional 30 minutes before being recooled to -78°C. A solution of diphenyl disulphide (460 mg, 2.1 mmol) in ether (10 ml) was added, resulting in the formation of a white suspension which disappeared during the following hour. The coolant was removed, the dry-ice condenser was replaced by a water condenser and the ammonia allowed to evaporate overnight. The resulting residue was partitioned between ether (60 ml) and water (25 ml), and the aqueous layer was separated and extracted with ether (40 ml). The combined ether fractions were washed with water (30 ml) and saturated aqueous sodium chloride solution (30 ml), and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave an orange oil which was purified by chromatography on Kieselgel G (60 g) with dichloromethane-benzene (50%) to give the α-*phenylthio ketone* (**14**) as a pale yellow solid (312 mg, 45%). Crystallisation from ether-pentane gave white needle-shaped crystals, mp 93-95°C. (Found: C, 68.60; H, 7.3; S, 9.85%; M^+, 332.14412 $C_{19}H_{24}O_3S$ requires C, 68.55; H, 7.2; S, 9.65%; M, 332.144607); $\nu_{max}(CHCl_3)$: 1710(s) cm^{-1}; $\delta_H(CDCl_3)$: 90MHz), 1.19(3H, s), 1.20-2.63(11H, m), 3.50(1H, d, J 13Hz), 3.84-4.00(4H, m), 7.15-7.45(5H, m); $\delta_c(CDCl_3$: 22.5MHz), 14.90(q), 22.48(t), 26.33(t), 29.74(t), 29.96(t), 36.68(t), 43 07(s), 46.70(d), 59.70(d), 64.96(t), 65.17(t), 112.3(s), 127.04(d), 128.83(d), 129.04(d), 131.86(d), 135.38(s), 206.46(s); m/z(%), 332(M$^+$, 17 6), 223(85.5), 161(6.5), 113(20.5), 99(100), 86(47.0), 73(14.5).

3′,4′,4′a,5′,8′,8′a-Hexahydro-5′-hydroxymethylene-8′a-methylspiro[1,3-dioxolane-2,1′(2′*H*)-naphthalen]-6′(7′*H*)-one(15). A solution of the ketal-enone (**12**) (362 mg, 1.63 mmol) and water (29 mg, 1.6 mmol) in anhydrous THF (10 ml) was added dropwise to a stirred solution of lithium (34 mg, 4.9 mmol) in anhydrous liquid ammonia (50 ml) under an argon atmosphere. Stirring was continued for a further 10 minutes, after which the excess lithium was destroyed by the careful addition of isoprene The ammonia was allowed to evaporate under a brisk stream of argon and the remaining THF was removed under reduced pressure. High vacuum (0.1 mm Hg) was applied to the resulting residue, with gentle warming, for 30 minutes. Anhydrous ether (25ml) was added to the remaining residue and the reaction mixture was cooled to -78°C A solution of freshly distilled methyl formate (1.47g, 24.5 mmol) in ether (5 ml) was added to the reaction mixture in a single portion, with stirring. Stirring was continued for a further 30 minutes at 0°C and then for 1 hour at room temperature. The reaction mixture was diluted with ether (50 ml), washed with 2M hydrochloric acid (2 x 20 ml) and extracted with 2M potassium hydroxide solution (30 ml). The basic aqueous fraction was separated and washed with ether (2 x 20 ml), acidified with 6M hydrochloric acid to Congo red, and extracted with chloroform (2 x 40 ml). The combined chloroform fractions were washed with water (20 ml), and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave a yellow oily residue which was purified by chromatography on Kieselgel G (25 g) with 3% ether in benzene as the eluent, to give the α-*hydroxymethylene ketone* (**15**) (66 mg, 16%) as a colourless oil. (Found: M^+, 252.13604. $C_{14}H_{20}O_4$ requires M, 252.136150);

$\nu_{max}(CHCl_3)$: 3600-3000(br, s), 1640(s), 1585(s) cm^{-1}; $\delta_H(CDCl_3$: 90MHz), 0.95(3H, s), 1.05-1.80(7H, m), 1.85-2.73(4H, m), 3.92-4.0(4H, m), 8.59(1H, m), 14.30(1H, br s, D_2O exchange); $\delta_c(CDCl_3$: 22.5MHz), 13.38(q), 22.37(t), 27.52(t), 28.88(t), 30.28(t), 35.43(t), 35.92(d), 41.23(s), 64.79(t),. 65.18(t), 107.86(s), 112.03(s), 183.49(s), 187.34(d); m/z(%) 252($\underline{M}^+$, 19.8), 190(31.4), 162(10.2), 137(11.5), 113(23.6), 99(85.2), 85(100).

3′,4′,4′a,7′,8′,8′a-Hexahydro-8′a-methyl-5′-(2-propenyl)spiro[1,3-dioxolane-2,1′(2′*H*)naphthalen]-6′(5′*H*)-one(16). A solution of the ketal enone (**12**) (7.93g, 35.7 mmol) and water (1.16 g, 64.3 mmol) in tetrahydrofuran (100 ml) was added dropwise to a stirred solution of lithium (0.87g, 124.3 mmol) in liquid ammonia (500 ml) at -33°C, in an argon atmosphere. The resulting solution was stirred for 10 minutes, then allyl bromide (43.0g, 0.36 mol) was added. The mixture was stirred for 1 hour, then the ammonia was allowed to evaporate in a stream of argon. The residue was partitioned between ether (100 ml) and water (50 ml). The aqueous layer was extracted with ether (50 ml), the combined ethereal extracts were washed successively with dilute hydrochloric acid (50 ml), water (50 ml), and brine (50 ml), then dried ($MgSO_4$). Removal of the solvent under reduced pressure gave a yellow oily product which was purified by column chromatography on Kieselgel G, using ethyl acetate-hexane (1:4) as eluent. The *propenylketone* (**16**) (7.99g, 85%) was obtained as colourless prisms, m.p. 72-73.5°C from ether (Found: C, 72.7; H, 9.15%; M^+, 264.17188. $C_{16}H_{24}O_3$ requires C, 72.6, H, 9.15%; M, 264.172534); $\nu_{max}(CHCl_3)$: 1700, 1632 cm^{-1}; $\delta_H(CDCl_3$; 400 MHz), 1.15(3H, s), 1.3-1.9(9H, m), 2.1-2.5(5H, m), 3.84(4H, m), 4.90(1H, dd, J 10, 1Hz), 4.94(1H, dd, J 20, 1Hz), 5.70(1H, m); $\delta_c(CDCl_3)$, 14.15, 22 49, 24.52, 29.82(x2), 30.22, 37.61, 42.12, 44.76, 49.54, 64.77, 64.99, 112.31, 115.97, 136.17, 211.34; m/z(%), 264(M^+, 9.1), 223(6.0), 210(5.1), 169(3.8), 112(21.9), 99(100), 86(93.6).

3′,4′,4′a,7′,8′,8′a-Hexahydro-5′-(2-oxoethyl)-8′a-methylspiro[1,3-dioxolane-2,1′(2′*H*)-naphthalen]-6′(5′*H*)-one(17). A stream of ozone was bubbled through a solution of the allylketone (**16**) (3.88g, 14.7 mmol) in anhydrous dichloromethane (500 ml) at -60°C for 45 minutes. The excess ozone was removed in a stream of nitrogen, then triphenylphosphine (6.0 g, 22.0 mmol) was added to the solution, which was stirred and allowed to warm to room temperature. The solvent was removed under pressure and the resulting residue was purified by flash chromatography using ethyl acetate-hexane (40:60) as eluent. The *keto-aldehyde* (**17**) (3.31g, 85%) obtained was recrystallised from ether, which gave colourless prisms, m.p. 77.5-79 5°C (Found· M^+, 266.1528. $C_{15}H_{22}O_4$ requires M, 266.151799); $\nu_{max}(CHCl_3)$, 1720, 1700 cm^{-1}; $\delta_H(CDCl$: 400 MHz), 1.30(3H, s), 1.37-2.00(9H, m), 2.3-2.6(3H, m), 2.75-3.00(2H, m), 3.93(4H, m), 9.85(1H, s); $\delta_c(CDCl_3)$, 13 67, 22.12, 24 96, 29.34, 29.56, 30.24, 36.87, 40.34, 42.00, 45.96, 64.57, 65.12, 111.67, 200.90, 210; m/z(%), 266(M^+, 4.9), 238(10.6), 209(10.2), 112(45.4), 99(80.6), 86(100), 69(11 8).

5′,5′a,7′,8′,9′,9′a-Hexahydro-5′a-methylspiro[1,3-dioxolane-2,6′(4′*H*)-naphtho[2,1-*b*]furan(11). A mixture of the keto-aldehyde (**17**) (2.76g, 10.38 mmol), acetic anhydride (7.5 ml) and glacial acetic acid (75 ml) was heated at reflux for 90 minutes. The cooled reaction mixture was poured on to ice (200 g) and extracted with ether (2 x 100 ml). The combined ether extracts were washed successively with saturated sodium bicarbonate solution (4 x 100 ml), water (2 x 50 ml), and brine (2 x 50 ml), then dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography, using ethyl acetate-hexane (2:3) as eluent, from which the *naphthofuran* (**11**) (77%) was obtained. Recrystallisation from ether gave colourless prisms, m.p. 51.3-52°C (Found: C, 72.35; H, 8.15%. M^+, 248.14127. $C_{15}H_{20}O_3$ requires C, 72.55, 8.12%. M, 248.141235); $\delta_H(CDCl_3$: 300 MHz) 0.90(3H, s), 1.20-1.45(2H, m), 1.60-1.75(6H, m), 2.50-

2.70(2H, m), 2.75-2.80(1H, m), 4.00(4H, m), 6.25(1H, d, J 1Hz), 7.25(1H, d, J 1Hz); δ_c ($CDCl_3$), 13.23, 20.16, 23.04, 23.96, 27.21, 30.45, 38.66, 42.15, 65.15(x2), 108.76, 112.61, 119.69, 140.59, 148.74; m/z(%), 248(M^+, 100), 187(17.4), 161(9.9), 148(85.9), 133(42), 113(69.9), 99(80.2), 86(87.7), 77(30.3), 69(30.2).

5′,5′a,7′,8′,9′,9′a-Hexahydro-5′a-methylspiro[1,3-dioxolane-2′,6′(4′*H*)-naphtho[2,1-*b*]furan-2-carboxaldehyde(19). Freshly distilled phosphorus oxychloride (3.0g, 19.6 mmol) was added dropwise to dimethylformamide (15 ml), with stirring, at 0°C. After 30 minutes at 0°C the reaction mixture was allowed to warm to room temperature and stirred at this temperature for 15 minutes before being recooled to 0°C. A solution of the ketal-furan (**11**) (2.41 g, 9.71 mmol) in dimethylformamide (20 ml) was then added dropwise. The resulting red solution was stirred for one hour and then poured onto an ice-water slurry (150 ml). The resulting mixture was added dropwise to ice-cold ammonium hydroxide solution, the pH was adjusted to 7 and then left overnight at 0°C. The resulting aqueous suspension was extracted with ether (3 x 80 ml) and the combined ethereal extracts were washed successively with 2M hydrochloric acid (2 x 30 ml), 2M sodium hydroxide (2 x 30 ml), water (75 ml), and saturated aqueous sodium chloride solution, and then dried ($MgSO_4$). Removal of the solvent under reduced pressure gave an orange solid residue which was purified by chromatography on Kieselgel G (120 g) with dichloromethane-hexane (1:9) as the eluent, to give the *naphthofuran ketalaldehyde* (**19**) as a yellow solid (2.31g, 86%). Crystallisation from ether or methanol gave pale yellow needles, mp 117°-118°C. (Found: C, 69.4; 69.45; H, 7.45, 7.35%; M^+, 276.13701. $C_{16}H_{20}O_4$ requires C, 69.5; H, 7.25%; M, 276.136150); ν_{max} ($CHCl_3$), 1655, 1597 cm^{-1}; δ_H($CDCl_3$, 400 MHz), 0.86(3H, s), 1.34-1.45(1H, m), 1.55-1.70(2H, m), 1.74-1.92(5H, m), 2.55-2.87(3H, m), 3.95(4H, m), 7.07(1H, s), 9.45(1H, s); δ_H($CDCl_3$), 13.19, 20.56, 22.70, 23.72, 26.54, 30.15, 38.39, 41.86, 65.06, 65.13, 112.0, 121.56, 124.13, 151.88, 157.50, 176.56; m/z(%), 276(M^+, 80), 248(8), 214(13), 176(21), 161(23), 113(57), 112(43), 100(47), 99(100), 86(90).

In another preparation the reaction mixture was added to dilute ammonium hydroxide solution, a very small excess of dilute hydrochloric acid was added and the mixture then allowed to stand at 0°C overnight. Extraction of the total product, followed by flash chromatography with ethyl acetate-hexane (2:3) as eluent, gave the keto aldehyde (**20**)(53%), followed by the ketal aldehyde (**19**)(37%).

4,5,5a,8,9,9a-Hexahydro-5a-methyl-6(7H)-oxonaphtho[2,1-b]furan-2-carboxaldehyde(**20**) was obtained from methanol as yellow prisms. m.p. 125.5-126.5°C (Found: C, 72.35; H, 6.85. $C_{14}H_{16}O_3$ requires C, 72.4; H, 6.95%); ν_{max}($CHCl_3$) 3020, 2950, 1700, 1670, 1598 cm^{-1}; δ_H($CDCl_3$: 300 MHz) 0.96(3H, s), 1.6-1.9(3H, m), 1.9-2.3(4H, m), 2.5-2.8(4H, m), 7.07(1H, s), and 9.40(1H, s); δ_c($CDCl_3$), 15.21, 20.29, 23.42, 25.62, 28.56, 36.75, 41.99, 47.55, 121.40 (br), 122.37, 152.17, 157.05, 176.76, 213.60.

5′,5′a,7′,8′,9′,9′a-Hexahydro-5′a-methyl-2′-(2-methyl-1-propenyl)spiro[1,3-dioxolane-2,6′(4′*H*)-naphtho[2,1-*b*]furan(21). A solution of n-butyl-lithium in hexanes (1.6M; 5.45ml) was added dropwise to a stirred suspension of isopropyltriphenylphosphonium iodide (4.26g) in tetrahydrofuran (40 ml) at 0°C. The resulting red solution was stirred at room temperature for 20 minutes, then cooled to 0°C, and a solution of the aldehyde (**19**) (2.1g) in tetrahydrofuran (40 ml) was added dropwise. The mixture was stirred at -2°C for 30 minutes, then filtered through Celite and the filtrate concentrated under reduced pressure. The residue was purified by column chromatography on Kieselgel G using 5% ethyl acetate in hexane as eluent. The *isopropylidene derivative* (**21**) (97%) was obtained as a colourless oil (Found: C, 75.35; H, 8.55%; M^+, 302.18765. $C_{19}H_{26}O_3$ requires C, 75.45; H, 8.65%; M, 302.188183); ν_{max} 1670, 1623 cm^{-1}; δ_H($CDCl_3$, 300

MHz), 0.90(3H, s), 1.2-1.5(2H, m), 1.6-2.0(6H, m), 1.86(3H, s), 1.96(3H, s), 2.5-2.7(3H, m), 3.9(4H, m), 6.0(2H, s); m/z(%), 302(M^+, 100), 262(17.2), 248(18), 241(12), 202(25), 190(29), 148(14), 113(36), 99(26), 86(28).

1-(5′,5′a,7′,8′,9′,9′a-Hexahydro-5′a-methylspiro[1,3-dioxolane-2,6′(4′*H*)-naphtho[2,1-*b*]-furan]-2′-yl)-2-methyl-1,2-propanediol(18).

A. A solution of the isobutenylfuran (**21**) (98 mg, 0.32 mmol) in a mixture of acetone (1 ml), water (0,5 ml) and t-butyl alcohol (1 ml), containing N-methylmorpholine N-oxide (54 mg, 0.46 mmol) and osmium tetroxide (3.5 mg, 0.014 mmol) was stirred at room temperature for 6 hours. A slurry composed of Florisil (1.0 g), sodium dithionite (100 mg), and water (1 ml) was then added. The resulting mixture was stirred for a further 20 minutes and then filtered through a pad of Celite. The filter cake was washed with acetone (2 x 5 ml) and the combined acetone washings were concentrated under reduced pressure. The resulting residue was applied directly to a chromatography column of Keiselgel G (35 g) with dichloromethane-ether (15:85) as the eluent, to give the *furan diol* (18) (35.7 mg, 34%) as a white waxy solid.

B. To a stirred solution of osmium tetroxide (100 mg, 0.39 mmol) in dry pyridine (5 ml), cooled to 0°C, the isobutenylfuran (**21**) (117 mg, 0.39 mmol) in pyridine (3 ml) was added. The reaction mixture was allowed to warm to room temperature and stirred for 16 hours, then a solution of sodium metabisulphite (500 mg) in water (2 ml) and pyridine (1 ml) was added, and stirring continued for a further 30 minutes. The pyridine was removed under reduced pressure below 35°C, and the resulting orange residue was taken up into ether (30 ml) and washed with water (10 ml). The aqueous fraction was separated and extracted with ether (2 x 20 ml). The combined organic fractions were washed with 4M hydrochloric acid (25 ml), water (25 ml), and saturated aqueous sodium chloride solution (25 ml), and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave a white foam which was purified by chromatography on Kieselgel G (65 g) with benzene-ether (2:1) as the eluent, to give *furan diol* (**18**) (97 mg, 74%) (Found: M^+, 336.19284. $C_{19}H_{28}O_5$ requires M, 336.193661); δ_H($DCDl_3$: 90MHz), 0.88(3H, s), 1.17(3H, s), 1.27(3H, s), 1.35-2.05(8H, m), 2.10-2.45(2H, br s, D_2O exchange), 2.55-2.95(3H, m), 3.95-4.10(4H, m), 4.40(1H, d, J 2.5 Hz), 6.20(1H, d, J 2.5Hz); m/z(%), 336(M^+, 3.4), 277(100), 233(4.4), 217(5.8), 133(22.4), 99(25.1), 86(20.2), 69(13.9), 59(15.7).

Some diol A (**22**)(12 mg, 9%) was also eluted (see the following experiment for the physical data).

4′a,5′,6′,6′a,8′,9′,10′,10′a-Octahydro-4′a-hydroxy-3′-(1′-hydroxy-1′-methylethyl)-6′a-methylspiro[1,3-dioxolane-2,7′-[7′*H*]naphtho[2,1-*b*]pyran]-2′(3′*H*)-one.

A. A mixture of the isobutenylfuran (**21**) (3.34g, 10.93 mmol), N-methylmorpholine N-oxide (2.45 g, 20.67 mmol), osmium tetroxide (60 mg, 0.3 mmol), t-butyl alcohol (40 ml), acetone (40 ml), and water (20 ml) was stirred at room temperature for 66 hours. Sodium metabisulphite (3g) and Florisil (15 g) were then added, the mixture was filtered through silica, and concentrated under reduced pressure. The residual oil was partially purified by flash chromatography using ether as eluent. The resulting yellow foam (2.75g) was dissolved in dichloromethane, the solution was cooled to 0°C, and treated with m-chloroperbenzoic acid (8.18 mmol). The mixture was stirred at room temperature for 3 hours, then washed successively with 10% sodium sulphite solution (15 ml), saturated sodium bicarbonate solution (20 ml), and brine (20 ml), then dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by column chromatography on Kieselgel G using ether-hexane (1:1) as eluent. Two isomeric diols were obtained:

Diol A (**22**)(1.04g, 27%) was obtained as colourless prisms from ethyl acetate, m.p. 178-182° (Found: C, 64.6; H, 8.15. $C_{19}H_{28}O_6$ requires C, 64.75; H, 8.0%); ν_{max} ($CHCl_3$) 3600-3200, 1660, 1600 cm^{-1}; δ_H($CDCl_3$, 400

MHz), 0.90(3H, s, H-14), 1.35, 1.45(6H, 2s, H-12 and H-13), 1.37-1.63(4H, m), 1.65-1.90(4H, m), 1.98-2.18(2H, m), 2.78-2.85(2H, m, H-10'a and OH), 3.85-4.05(5H, m, H-4, H-5 and H-3'), 5.38(1H, OH), 5.81(1H, d J 1.8Hz, H-1'); $\delta_c(CDCl_3)$, 14.50, 21.96, 22.42, 26.60, 26.62, 26.77, 30.10, 35.59, 43.92, 45.86, 65.29, 65.32, 73.54, 83.90, 92.83, 112.05, 121.67, 164.73, and 194.95; m/z(%) 352(M^+, 3), 294(40), 277(14), 276(46), 235(14), 204(10), 113(22), 112(10), 100(11), 99(100), 86(64), 69(13).

Diol B (**23**) (1.0g, 26%) was obtained from ether as colourless prisms, m.p. 144-145°C (Found: C, 64.95; H, 8.2%); ν_{max} ($CHCl_3$), 3600-3200, 1660, 1600 cm^{-1}; $\delta_H(CDCl_3$, 400MHz), 0.93(3H, s, H-14'), 1.24, 1.26(6H, 2s, H-12', H-13'), 1.36(1H, m), 1.45-1.63(4H, m), 1.65-1.80(2H, m), 1.88-2.10(3H, m), 2.70(1H, dt, J 11.6, 2.2 Hz, H-10'a), 2.82(1H, br s, OH), 3.95(4H, m, H-4 and H-5), 4.15(1H, br s, OH), 4.24(1H, s, H-3'), 5.76(1H, d, J 2Hz, H-1'); $\delta_c(CDCl_3)$, 14.67, 21.90, 22.43, 24.26, 26.24, 26.47, 29.92, 36.43, 44.11, 45.35, 65.24, 65.28, 72.47, 76.87, 93.76, 111.94, 122.33, 164.29, and 198.78, m/z(%), 352(M^+, 2), 294(7.6), 276(2.1), 113(14.4), 112(6.1), 100(8.9), 99(100), 86(70.1).

B. m-Chloroperbenzoic acid (95%; 31 mg, 0.17 mmol) was added to a stirred solution of the furan diol (**18**) (50mg, 0.15 mmol) in anhydrous dichloromethane at 0°C. After 30 minutes at 0°C the reaction mixture was allowed to warm up to room temperature and was then stirred for a further 4 hours. The mixture was then diluted with dichloromethane (20 ml) and washed successively with 10% sodium sulphite solution (5 ml), saturated aqueous sodium bicarbonate solution (2 x 5 ml), water (10 ml), and then dried ($MgSO_4$). Removal of the solvent under reduced pressure followed by chromatography on Kieselgel G (45g) gave diol A (**22**) (30 mg, 57%) and diol B (**23**) (19 mg, 36%), whose infrared, n.m.r. and mass spectra were identical with those prepared by procedure A. Diol A (Found: C, 64.5; H, 7.9%; M^+, 352.18951. Diol B (Found: C, 64.65; H, 8.05%, M^+, 352.18799). $C_{19}H_{28}O_6$ requires C, 64.75; H, 8.0%; M, 352.188575).

3',4',7',7'a,9',10',11',11'a-Octahydro-4',4',7'a-trimethylspiro[1,3-dioxolane]-2,8'(6'*H*)-2'*H*-3',5'a]epoxynaphth[2,1-b]oxepin]-2'-one(3'β,5'aβ,7'aβ,11'aα) (**24**). A mixture of diol A (**22**) (50 mg), anhydrous copper sulphate (200 mg), toluene p-sulphonic acid (2 mg), and benzene (15 ml) was stirred at room temperature for 2 hours. The reaction mixture was then filtered through a sintered glass funnel and the collected solid was washed with ether (10 ml) and benzene (10 ml). The solvent was removed from the filtrate under reduced pressure, and the residue purified by flash chromatography, using ether: benzene (1:9) as eluent. The β-*pyrone ketal* (**24**) (40.7 mg, 86%) was obtained from ether-pentane as colourless prisms, m.p. 104.5-106 5°C (Found: C, 68.2; H, 7.85%; M^+, 334.17788. $C_{19}H_{26}O_5$ requires C, 68.25; H, 7.85%; M, 334.178012); $\nu_{max}(CHCl_3)$, 1670, 1600cm^{-1}; $\delta_H(CDCl_3$, 300 MHz), 0.98(3H, s, H-7'b), 1.15(3H, s, H-4'b), 1.3(1H, m), 1.41(3H, s, H-4'a), 1.55-1.65(3H, m), 1.65-1.80(3H, m), 1.9(1H, m), 2.0-2.25(2H, m), 2.60(1H, dt, J 11.8 and 2.8 Hz, H-11'a), 3.95-4.10(4H, m), 4.20(1H, d, J 1Hz, H-3'), and 5.80(1H, m, H-1'); $\delta_c(CDCl_3)$, 15.36, 21 83 x 2, 22 98, 26.38, 29.07, 29.71, 29.81, 43.05, 44.49, 65.25, 65.28, 80.06, 86 91, 103.54, 111.92, 120.68, 166.97 and 194.59; m/z(%), 334(M^+, 1.2), 277(8.4), 276(43.8), 204(12.7), 113(21.7), 112(7.9), 99(100), 91(12.3), 86(91 3).

In another preparation the β-pyrone ketal (**24**) was observed to be contaminated by the related ketone (possibly **26**, but stereochemistry not elucidated), which proved to be inseparable by column or flash chromatography. Separation was achieved by hplc on a Technicol Zorbax CN10μ, 8 x 250 mm column with hexane-isopropyl alcohol (9:1) as eluent, which gave the β-pyrone ketal (**24**) (74%), identical with that described above, and 2,3,4,5a,6,7,7a,8,9,10,11,11a-*dodecahydro*-4,4,7a-*trimethyl*-3,5a-*epoxynaphth*[2,1-b]*oxepin*-2,8-*dione* (**26**) (5%)

as a colourless, amorphous solid, m.p. 61-65°(Found: M^+, 290.15242. $C_{17}H_{22}O_4$ requires M, 290.151799); ν_{max} 1705, 1685, 1675 cm^{-1}; δ_H($CDCl_3$: 400 MHz), 1.20(3H, s), 1.25(3H, s), 1.45(1H, m), 1.55(3H, s), 1.60-1.85(2H, m), 1.85-2.00(3H, m), 2.15(1H, s), 2.38(1H, m), 2.60-2.75(2H, m), 2.90(1H, m), 4.35(1H, d, J 1 Hz), 5.85(1H, m); m/z(%) 290(M^+, 12.1), 232(20.5), 219(100), 191(12.9), 173(22.9), 121(14.1), 91(29.0), 79(21.8).

3′,4′,7′,7′a,9′,10′,11′,11′a-Octahydro-4′,4′,7a′-trimethylspiro[1,3-dioxolane]-2,8′(6′*H*)-2*H*-3′5′a-epoxynaphth[2,1-*b*]oxepin-2′-one(3′α,5′aα,7′aβ,11′aα)(25). A mixture of diol B (**23**) (50 mg), anhydrous copper sulphate (200 mg), toluene p-sulphonic acid (2 mg), and benzene (15 ml) was stirred at room temperature for 3.5 hours. The reaction mixture was then filtered through a sintered glass funnel and the collected solid was washed with ether (10 ml) and benzene (10 ml). The solvent was removed from the filtrate under reduced pressure and the residue was purified by column chromatography on Kieselgel G using ether-benzene (1:9) as eluent. The β-*pyrone ketal* (**25**) (31.4 mg, 67%) was obtained from ether-ethyl acetate as colourless needles, m.p. 176-180°C (Found: C, 68.25; H, 7.95. $C_{19}H_{26}O_5$ requires C, 68.25; H, 7.85%); ν_{max} 1670, 1600 cm^{-1}; δ_H ($CDCl_3$, 300 MHz), 1.10(3H, s, H-7′b), 1.20, 1.40(2 x 3H, 2s, H-4′a and H-4′b), 1.45-1.85(8H, m), 1.90-2.23(2H, m), 2.87(1H, dt, J 11.3, 3Hz, H-11′a), 4.0-4.1(4H, m, H-4 and H-5), 4.28(1H, s, H-3′), and 5.75(1H, d J 3Hz, H-1′); δ_c($CDCl_3$) 20.61(C-7′b), 21.36, 21.63, 25.91(C-9′, 10′, 11′), 23.13m 28.89(C-4′a and 4′b), 28.12, 28.44(C-6′ and 7′), 39.70(C-7′a), 42.62(C-11′a), 65.88(C-4 and C-5), 77.45(C-4′), 88.22(C-3′), 103.97(C-5′a), 112.89(C-8′), 119.9(C-1′), 171.47(C-11′b), and 196.09(C-2′); m/z(%) 334(M^+, 2.9), 277(14.4), 276(100), 204(21.8),. 113(25.3), 112(10.4), 100(10.5), 99(55.3).

Also obtained was 6′,6′a,8′,9′,10′,10′a-*hexahydro*-3′-(1-*hydroxy*-1-*methylethyl*)-6′a-*methylspiro*[1,3-*dioxolane*-2,7′(7′H)*naphtho*[2,1-b]*pyran*-2′(3′H)-*one*(**27**) (8.4mg, 18%), which crystallised from ether-pentane as colourless prisms, m.p. 133-136°C (Found: C, 67.95; H, 7.9. $C_{19}H_{26}O_5$ requires C, 68.25; H, 7.85%); ν_{max}, 3600-3200, 1720, 1670 cm^{-1}; δ_H($CDCl_3$), 0.99(3H, s, H-14′), 1 25, 1.35(2 x 3H, 2s, H-12′ and H-13′), 1.5-1.7(4H, m), 1.7-1.9(2H, m), 2.14(1H, dd, J 18.3, 6.9 Hz, H-6′), 2.88(1H, ddd, J 11.7, 4, 2Hz, H-10′a), 3.65(1H, s, OH), 3.9-4.05(4H, m, H-3 and H-4), 4.20(1H, s, H-3′), 5.63(1H, ddd, J 6.8, 2.9, 2 Hz, H-5′), 5.95(1H, m, H-1′); δ_c($CDCl_3$), 15.02(C-14′), 21.60, 22.03, 26.50(C-8′, C-9′, C-10′), 24.70, 30.24(C-12′, C-13′), 29.45(C-6′, 42.78(C-10′a), 43.71(C-6′a), 65.01, 65.12(C-4, C-5), 73.41(C-11′), 84.16(C-3′), 111.74(C-7′), 112.39(C-5′), 119.16(C-1′)., 154.55(C-10′b).

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