Pergamon

Tetrahedron 54 (1998) 243–256

TETRAHEDRON

Aspects of the Chemistry of Dioxolanes: Synthesis of C-Nucleoside Analogues

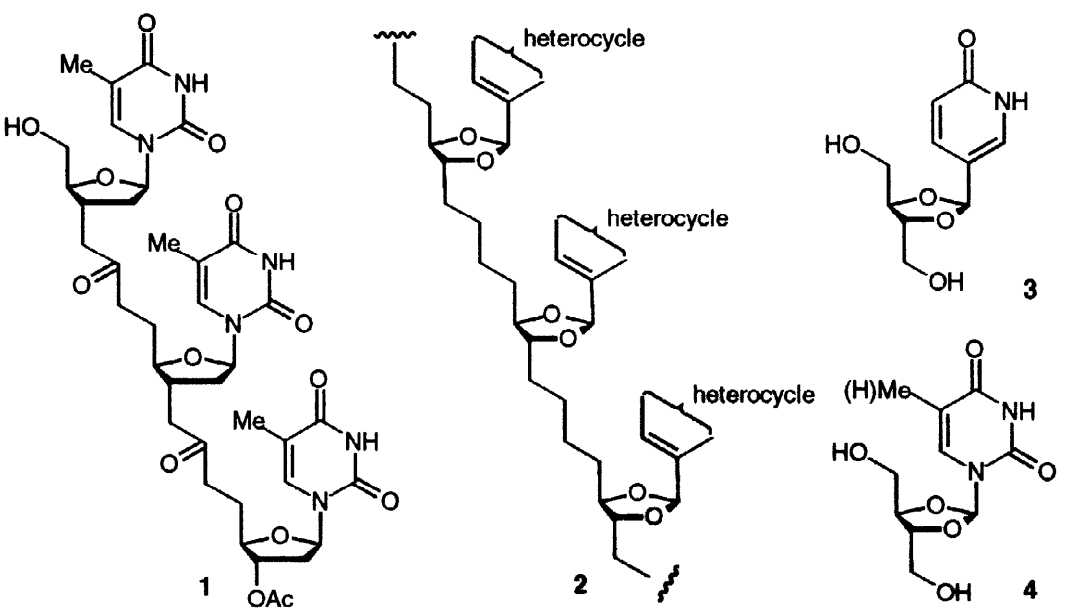
Ben J. Mellor, Patricia E. Murray and Eric J. Thomas*

The Department of Chemistry, The University of Manchester, Manchester M13 9PL, U.K.

Received 7 October 1997; accepted 30 October 1997

Abstract: Chiral 2-formyl and 2-(1-oxoalkyl)-1,3-dioxolanes have been prepared by ozonolysis of the corresponding alkenes and by oxidation of 2-(1-hydroxyalkyl)-1,3-dioxolanes, which are readily available from 2-(tributylstannyl)dioxolanes, and taken through to αβ-unsaturated esters by condensation with stabilized ylids. The (4'*S*,5'*S*)-1-benzyl-5-[4,5-bis(ethoxycarbonyl)-1,3-dioxolan-2-yl]-2-pyridone **47** was prepared as an analogue of a C-nucleoside, but was found to be unstable.

The synthesis of analogues of oligonucleotides in which the polar phosphate groups have been replaced by non-polar and preferably achiral substituents is of considerable interest at present, for example in the context of anti-sense therapy.[1] Amongst the many nucleotide analogues which have been synthesized are compounds in which the phosphates have been replaced by three-carbon fragments, e.g. the C-linked 3'-acetyl trinucleotide **1**.[2] As an extension of this work, the acetals **2** were identified as possible targets for synthesis. These compounds are structurally homologous with deoxyribonucleotides even though all three components, the base, the ribose and the phosphate, have been modified, and can be regarded as oligomers of 2-substituted-1,3-dioxolanes, e.g. **3**.



1 2 3 4

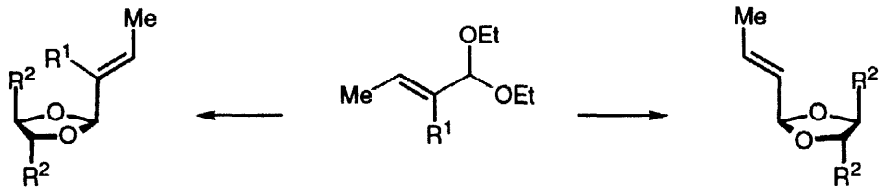
0040-4020/98/$19.00
PII: S0040-4020(97)10274-5

The 2-substituted 1,3-dioxolanes **4** have been synthesized recently as analogues of nucleosides and their anti-viral activities were evaluated.[3] The publication of his work prompts us to disclose our preliminary results concerned with the synthesis of 2-substituted dioxolanes including the 2-pyridone **3**.

Two approaches were investigated for the synthesis of the 2-substituted dioxolanes, namely the modification of 2-(1-oxoalkyl)-1,3-dioxolanes and the preparation of the dioxolanes directly from heterocyclic aldehydes. We used both the (*S,S*)- and (*R,R*)-diethyl tartrates as starting materials for our work since the anti-viral activity of both enantiomeric series of dioxolanes could be of interest.

RESULTS AND DISCUSSION

Initial studies were concerned with the synthesis of 2-(1-oxoalkyl)-1,3-dioxolanes by the oxidative cleavage of 2-alkenyl-1,3-dioxolanes. Several chiral 2-alkenyl-1,3-dioxolanes have been reported in the literature and the diastereoselectivities of their reactions with achiral reagents have been described.[4] Having prepared the 2-(1-oxoalkyl)-1,3-dioxolanes, it was intended to modify their 2-substituents to introduce a range of C-attached heterocycles. The 2-alkenyl-1,3-dioxolanes **7** - **15** were therefore prepared by acetal exchange of the butenal acetals **5** and **6**[5] with (*S,S*)-and (*R,R*)-diethyl tartrates followed by reduction and OH-protection.[6,7]

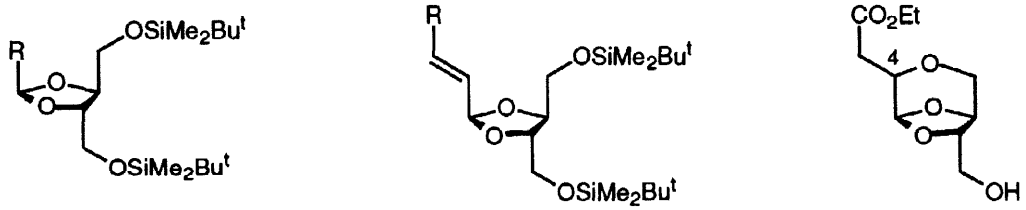


10/11 R^1 = H, Me R^2 = CO_2Et
12/13 R^1 = H, Me R^2 = CH_2OH
14 R^1 = H, R^2 = Bn
15 R^1 = Me, R^2 = $CH_2OSiMe_2Bu^t$

5 R^1 = H
6 R^1 = Me

7 R^2 = CO_2Et
8 R^2 = CH_2OH
9 R^2 = CH_2OSiMe_2Bu

Ozonolysis of the 2-propenyldioxolane **9** gave the aldehyde **16** which was reduced to the alcohol **17** using sodium borohydride and condensed with $Ph_3P{=}CHCO_2Et$ and $Ph_3P{=}CH_2$ to give the 2-alkenyl-1,3-dioxolanes **18** and **19**, better yields being obtained with the stabilized ylid. Of interest was the observation that deprotection of the αβ-unsaturated ester **18** using tetrabutylammonium fluoride was accompanied by conjugate addition and gave the tricyclic acetal **20** as a single diastereoisomer although the configuration at C(4) was not established. If this conjugate addition could be reversed, it would provide a way of differentiating between the two hydroxymethyl groups.

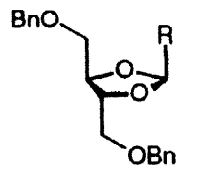


16 R = CHO
17 R = CH_2OH

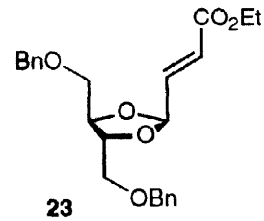
18 R = CO_2Et
19 R = H

20

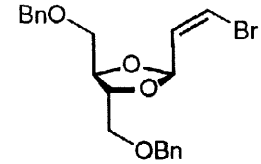
The (*R*,*R*)-4,5-bis(benzyloxymethyl)dioxolanyl aldehyde **21** was also prepared by ozonolysis, in this case, of the 2-alkenyl-1,3-dioxolane **14**. The aldehyde was reduced to the alcohol **22** and condensed with $Ph_3P{=}CHCO_2Et$ and $Ph_3P{=}CHBr$ to give the αβ-unsaturated ester **23** and the (*Z*)-vinyl bromide **24**, respectively. As before better yields were obtained with the stabilized ylid.



21 R = CHO
22 R = CH_2OH

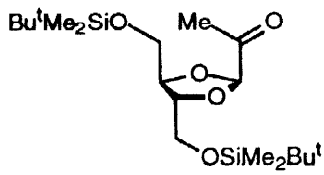


23

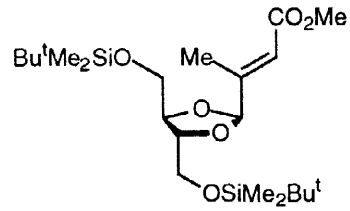


24

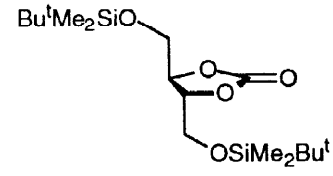
With a view to the introduction of branched substituents at C(2), the methyl ketone **25** was prepared by ozonolysis of the alkene **15**. As with the aldehydes **16** and **21**, efficient Wittig reactions were carried out with stabilized phosphoranes, e.g. $Ph_3P{=}CHCO_2Me$ gave the αβ-unsaturated ester **26**. However on standing in air, the ketone **25** was transformed into the carbonate **27**, perhaps *via* fragmentation of the hydroperoxide generated by autoxidation of its more substituted enol, and attempts to oxidize selectively the methyl groups of the ketone **25** or the unsaturated ester **26**, *en route* to the nucleoside analogue **3**, gave rise to complex mixtures of products.



25

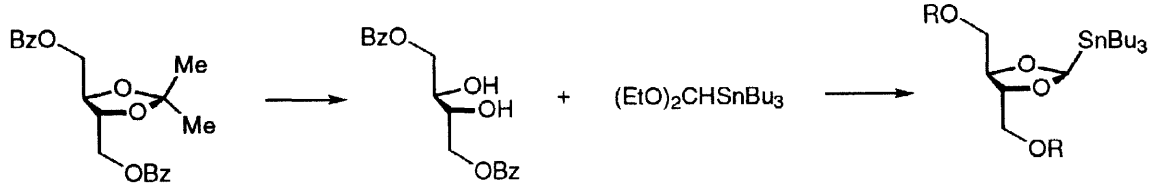


26



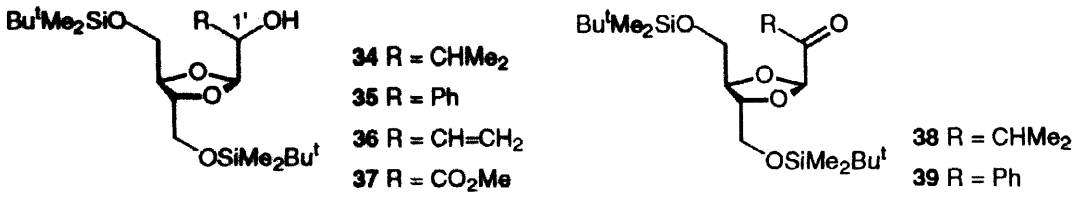
27

A second synthesis of 2-(1-oxoalkyl)-1,3-dioxolanes was developed from the 2-(tributylstannyl)-1,3-dioxolane **31** which was prepared from the (diethoxymethyl)tributylstannane **30** and diol **29**.[8] Preliminary attempts to carry out palladium(0) catalysed reactions of this α,α-dialkoxyalkylstannane with vinylic halides were not succcessful, and so the stannane was converted into its *tert*-butyldimethylsilyloxy analogue **33**. Transmetallation of this stannane using butyllithium followed by the adddition of an aldehyde gave the 2-(1-hydroxyalkyl)-1,3-dioxolanes **34** - **37**, albeit as mixtures of epimers at C(1'). Oxidation of the isopropyl and phenyl alcohols **34** and **35** then gave the corresponding ketones **38** and **39**.



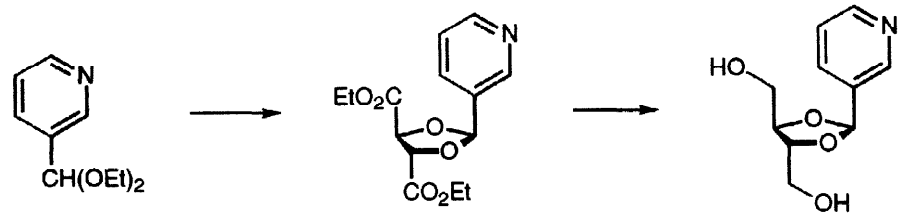
28 **29** **30**

31 R = Bz
32 R = H
33 R = $SiMe_2Bu^t$



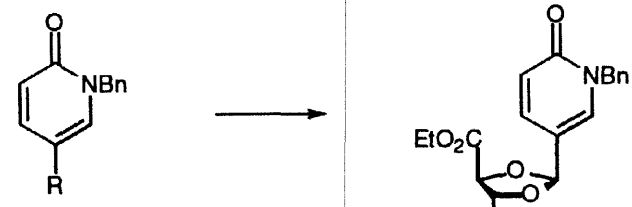
Although this work had given two routes to 2-(1-oxoalkyl)-1,3-dioxolanes, the oxidation of these compounds, e.g. using selenium dioxide, was found to give mixtures of products, and so the synthesis of dioxolanyl nucleoside analogues, e.g. **3**, from the 2-(1-oxoalkyl)-1,3-dioxolanes **25** or **38**, was not continued.

To evaluate the direct formation of C-nucleoside analogues, e.g. **3**, by acetal formation using heteroaromatic aldehydes, the 2-(3-pyridinyl)-1,3-dioxolane **41** was prepared from the diethoxyacetal **40**[9] and (*S*,*S*)-diethyl tartrate. Reduction gave the bis(hydroxymethyl)-1,3-dioxolane **42** but attempts to take this through to the C-nucleoside analogue **3** by the preparation and rearrangement of its *N*-oxide were unsuccessful.



40 **41** **42**

N-Benzylnicotinic acid **43**[10] was therefore converted into the aldehyde **46** by a reduction - oxidation sequence. When this aldehyde was heated under reflux in benzene with an excess of (*S*,*S*)-diethyl tartrate and a catalytic amount of pyridinium toluene *p*-sulfonate with removal of the water formed using a Dean-Stark trap, a low yield of the acetal **47** could be isolated by rapid HPLC of the product mixture. The acetal **47** was identified on the basis of its spectroscopic data, but it was found to be very unstable to chromatography, the low yield of isolated material being attributed to extensive acid catalysed decomposition on work-up.



43 R = CO$_2$H
44 R = COCl
45 R = CH$_2$OH
46 R = CHO

47

CONCLUSIONS

This work has resulted in the synthesis of several chiral 2-alkenyl and 2-(1-oxoalkyl)-1,3-dioxolanes including a synthesis of the latter compounds from the 2-tributylstannyl-1,3-dioxolane **33**. However, oxidation

of the methyl or isopropyl ketones **25** and **38**, or the αβ-unsaturated ester **26**, did not provide intermediates for the synthesis of C-nucleoside analogues. The dioxolane **47** was prepared from the aldehyde **46** but the instability of this acetal precluded reduction of the ethoxycarbonyl groups to complete a synthesis of the 2-(2-pyridonyl)-dioxolane **3**. The instability of **47** must be due to stabilization of the carbonium ion formed by acid-catalysed ring-opening of the acetal by the lone-pair of electrons on nitrogen, and although this effect is significantly less pronounced for the 1,3-dioxolane **4**, it would appear to limit the nature of the functionality which can be tolerated at C(2) of the dioxolane ring in these systems. Further work should focus on dioxolanyl analogues of showdomycin and similar C-nucleosides with strongly electron-withdrawing substituents at C(2).[11]

EXPERIMENTAL

All non-aqueous reactions were performed under an atmosphere of dry argon or nitrogen. Proton nuclear magnetic resonance spectra were recorded on Varian Unity 500 (500 MHz), Varian XL 300 (300 MHz), Bruker AC 300 (300 MHz) and Varian Gemini 200 (200 MHz) spectrometers in chloroform-d_1 unless otherwise stated. Carbon nuclear magnetic resonance spectra were recorded on a Bruker AC 300 MHz spectrometer operating at 75 MHz. Infrared spectra were recorded on a Perkin-Elmer 1710 FT spectrometer as evaporated films unless otherwise stated. Mass spectra were recorded on Kratos MS 25 (low resolution) and Kratos Concept-1S (high resolution) spectrometers using electron impact (EI), chemical ionisation (CI) or fast atom bombardment (FAB) modes of ionization. Optical rotations were measured using an Optical Activity AA 100 polarimeter with specific rotations determined at 20 °C. Chromatography refers to flash column chromatography and was carried out using May and Baker Sorbsil C60 silica gel (40-60 μ) as the stationary phase. Preparative reverse phase high performance liquid chromatography (HPLC) was carried out on a Gilson apparatus using a Rainin Dynamax 60A C18 column with dimensions of 21.4 mm x 250 mm using UV detection.

Light petroleum refers to the fraction which distils between 40 °C and 60 °C, ether refers to diethyl ether, and THF to tetrahydrofuran. All solvents were dried and distilled before use. The (*E*)-2-propenyl-4,5-bis(ethoxycarbonyl)-1,3-dioxolanes **7** and **10** were prepared from 1,1-diethoxy-2-butene[5] and either (*R,R*)- or (*S,S*)-diethyl tartrate heated under reflux in toluene in the presence of a catalytic amount of pyridinium toluene *p*-sulfonate (distilled yields *ca.* 80%).[6]

(4S,5S- and 4R,5R,1'E)-4,5-Bis(hydroxymethyl)-2-prop-1'-enyl-1,3-dioxolanes **8** *and* **12**

A solution of the ester **10**[6] (5.09 g, 19.7 mmol) in THF (40 cm^3) was added to a cooled solution of lithium aluminium hydride in THF (1 M; 53 cm^3, 53 mmol). The reaction mixture was warmed to room temperature and stirred for 3 h, cooled to 0 °C, and water (2 cm^3), sodium hydroxide (1 M; 2 cm^3) then water (6 cm^3) were added dropwise. The mixture was warmed to room temperature, stirred for 1 h, filtered and the residue was extracted with dichloromethane and methanol (4:1). The organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue using cyclohexane: ethyl acetate (1:3) as eluent gave the (4*R*,5*R*)-enantiomer of the *title compound* **12** (2.43 g, 71 %), $[\alpha]_D$ - 4.6 (c 6.5, CH_3OH); (Found: $M^+ + H$, 175.0963. $C_8H_{15}O_4$ requires *M*, 175.0970); ν_{max}/cm^{-1} 3386, 2920, 1679, 1449, 1379, 1119, 1042 and 961; δ_H (methanol-d_4) 1.82 (3 H, dd, *J* 6.5, 1.5, 3'-H_3), 2.05 (2 H, s, 2 x OH), 3.74 (4 H, m, 4-CH_2 and 5-CH_2), 3.98 (2 H, m, 4-H and 5-H), 5.42 (1 H, d, *J* 6.5, 2-H), 5.57 (1 H, ddq, *J* 15, 6.5, 1.5, 1'-H) and 6.02 (1 H, dq, *J* 15, 6.5, 2'-H); δ_C (methanol-d_4) 17.9, 63.5, 63.9, 80.2, 80.6, 105.8, 129.9 and 133.7; *m/z* (CI) 192 ($M^+ + 18$, 25 %) and 175 (100). The (4*S*,5*S*)-enantiomer of the title compound **8** was similarly prepared.

(4S,5S,1'E)-4,5-Bis(tert-butyldimethylsilyloxymethyl)-2-prop-1'-enyl-1,3-dioxolane **9**

tert-Butyldimethylsilyl chloride (0.65 g, 4.3 mmol) in *N,N*-dimethylformamide (5 cm^3) and imidazole 90.61 g, 8.96 mmol) in *N,N*-dimethylformamide (5 cm^3) were added to a solution of the diol **8** (0.13 g, 0.76 mmol) in *N,N*-dimethylformamide (20 cm^3) at 0 °C and the mixture stirred for 19 h at room temperature. Ethyl acetate (20 cm^3) was added and the solution washed with brine (3 x 20 cm^3). The washings were extracted with ethyl acetate and the organic extracts dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue using light petroleum: chloroform: ethyl acetate (6:3:1) as eluent gave the *title compound* **9** (0.28 g, 91%), $[\alpha]_D$ +2.6 (*c* 8.05 in MeOH) (Found: $M^+ + H$, 403.2683, $C_{20}H_{43}O_4Si_2$ requires *M*, 403. 2700); ν_{max}/cm^{-1} 1682, 1473, 1390, 1362, 1256, 1099, 962 and 838; δ_H 0.07 (12 H, s, 4 x MeSi), 0.87 (18 H, s, 2 x Me_3CSi), 1.73 (3 H, dd, *J* 6.5, 1.5, 3'-H_3), 3.67 - 4.05 (6 H, m, 4-H, 5-H, 4-CH_2 and 5-CH_2), 5.34 (1 H, dd, *J* 7, 0.5, 2-H), 5.49 (1 H, ddq, *J* 15, 7, 1.5, 1'-H) and 5.91 (1 H, ddq, *J* 15, 0.5, 6.5, 2'-H); *m/z* (CI) 403 ($M^+ + 1$, 100%).

(4S,5S,1'E)-4,5-Bis(ethoxycarbonyl)-2-(1-methylprop-1-enyl)-1,3-dioxolane **11**

A mixture of the unsaturated acetal **6**[5] (3.21 g, 20.3 mmol), pyridinium toluene *p*-sulfonate (0.5 g, 1.99 mmol) and (*S,S*)-diethyl tartrate (4.25 g, 20.6 mmol) in benzene (60 cm^3) was heated under reflux using a Dean-Stark trap. After cooling, distillation of the residue using a Kügelröhr apparatus gave the *title compound* **11** (4.61 g, 83 %), b.p. 200 °C/1 mmHg (Found: $M^+ + H$, 273.1334. $C_{13}H_{21}O_6$ requires *M*, 273.1338); $[\alpha]_D$ +4.36 (*c* 4.35, $CHCl_3$); ν_{max}/cm^{-1} 1755, 1680, 1215, 1123, 1095, 1031, 954 and 832; δ_H 1.35 (6 H, t, *J* 7, 2 x CH_2CH_3), 1.7 (6 H, m, 3'-H_3 and 1'-CH_3), 4.30 (4 H, q, *J* 7, 2 x CH_2CH_3), 4.72 and 4.84 (each 1 H, d, *J* 4, 4-H and 5-H), 5.48 (1 H, s, 2-H) and 5.84 (1 H, m, 2'-H); δ_C 9.4 13.3, 14.1, 61.9, 77.0, 77.3, 110.6, 128.9, 131.1, 161.7, 169.1 and 169.9; *m/z* (CI) 290 ($M^+ + 18$, 100%) and 273 (90).

(4R,5R,1'E)-4,5-Bis(hydroxymethyl)-2-(1-methylprop-1-enyl)-1,3-dioxolane **13**

A solution of the bis(ethoxycarbonyl)dioxolane **11** (5.83 g, 21.4 mmol) in THF (25 cm^3) was added to a cooled stirred suspension of lithium aluminium hydride (7.56 g, 199 mmol) in THF (150 cm^3). The mixture was allowed to warm to room temperature and was stirred for 2.25 h, then cooled to 0 °C, and water (7.6 cm^3), saturated aqueous sodium hydrogen carbonate (7.6 cm^3) and water (22.8 cm^3) were added dropwise. The mixture was warmed to room temperature, stirred for 1.5 h, filtered, and the solid residue was extracted with dichloromethane: methanol (4:1). The organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate as eluent gave the *title compound* **13** (3.67 g, 91 %) (Found: M^+, 188.1050. $C_9H_{16}O_4$ requires *M*, 188.1049); $[\alpha]_D$ +6.4 (*c* 2.5, $CHCl_3$); ν_{max}/cm^{-1} 3399, 1681, 1383, 1342, 1231, 1122, 1043, 968 and 830; δ_H (methanol-d_4), 1.68 (6 H, m, 3'-H_3 and 1'-CH_3), 3.7 (4 H, m, 4-CH_2 and 5-CH_2), 4.0 (2 H, m, 4-H and 5 -H), 5.30 (1 H, s, 2-H) and 5.73 (1 H, qd, *J* 6.5, 1, 2'-H); δ_C (methanol-d_4), 9.7, 13.1, 63.2, 63.6, 80.3, 80.4, 109.1, 127.1 and 134.4; *m/z* (CI) 206 ($M^+ + 18$, 68%) and 189 (100).

(4R,5R,1'E)-4,5-Bis(benzyloxymethyl)-2-prop-1'-enyl-1,3-dioxolane **14**

A solution of the diol **12** (2.43 g, 13.9 mmol) in THF (10 cm^3) was added to a suspension of NaH (1.01 g, 42 mmol) in THF (20 cm^3) at 0 °C. The reaction mixture was stirred for 1 h at room temperature, then cooled to 0 °C and tetrabutylammonium iodide (0.19 g, 0.51 mmol) and benzyl bromide (7.18 g, 42 mmol) were added. The solution was stirred at room temperature for 20 h, then cooled to 0 °C and water (5 cm^3) was added. The mixture

was warmed to room temperature, diluted with ether (15 cm^3) and the organic phase extracted with water (3 x 20 cm^3). The aqueous extracts were extracted with ether (3 x 15 cm^3), and the combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue using cyclohexane: ethyl acetate (7:1) as eluent gave the *title compound* **14** (4.63 g, 94 %) (Found: M^+ + H, 355.1906. $C_{22}H_{27}O_4$ requires *M*, 355.1909); $[\alpha]_D$ -1.95 (*c* 0.69, $CHCl_3$); ν_{max}/cm^{-1} 3030, 1680, 1497, 1453, 1366, 1115, 1028, 962, 737 and 698; δ_H 1.73 (3 H, dd, *J* 6, 1.5, 3'-H_3), 3.59 (4 H, m, 4-CH_2 and 5-CH_2), 4.1 (2 H, m, 4-H and 5-H), 4.56 (4 H, s, 2 x CH_2Ph), 5.36 (1 H, d, *J* 7.5, 2-H), 5.51 (1 H, ddq, *J* 15, 7.5, 1.5, 1'-H), 5.95 (1 H, dq, *J* 15, 6, 2'-H) and 7.3 (10 H, m, ArH); *m/z* (CI) 372 (M^+ + 18, 40 %) and 355 (100).

*(4*R*,5*R*,1*'E*)-4,5-Bis(*tert*-butyldimethylsilyloxymethyl)-2-(-1-methylprop-1'-enyl)-1,3-dioxolane* **15**

tert-Butyldimethylsilyl chloride (14.84 g, 98.5 mmol) in *N,N*-dimethylformamide (20 cm^3) and imidazole (8.88 g, 0.13 mol) in *N,N*-dimethylformamide (20 cm^3) were added to a stirred solution of the diol **13** (3.87 g, 20.5 mmol) in *N,N*-dimethylformamide (60 cm^3) at 0 °C. The reaction mixture was stirred for 14 h at room temperature, diluted with ethyl acetate (30 cm^3) and washed with brine (3 x 20 cm^3). The aqueous washings were extracted with ethyl acetate (5 x 20 cm^3), and the combined organic extracts dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue using light petroleum: ethyl acetate (10:1) as eluent gave the *title compound* **15** (5.0 g, 59 %) (Found: M^+, 416.2785. $C_{21}H_{44}O_4Si_2$ requires *M*, 416.2778); $[\alpha]_D$ -5.0 (*c* 12.9, $CHCl_3$); ν_{max}/cm^{-1} 1256, 1096, 837 and 778; δ_H 0.10 (12 H, s, 4 x MeSi), 0.93 (18 H, s, 2 x Me_3CSi), 1.68 (6 H, m, 3'-H_3 and 1'-CH_3), 3.73 - 4.12 (6 H, m, 4-H, 5-H, 4-CH_2 and 5-CH_2), 5.32 (1 H, s, 2 -H) and 5.73 (1 H, qd, *J* 6.5, 1, 2'-H); δ_C -5.4, -5.3, 9.6, 13.1, 18.3, 25.9, 26.0, 63.9, 64.0, 78.7, 78.9, 108.1, 126.5 and 132.96; *m/z* (CI) 434 (M^+ + 18, 1%), 418 (30) and 417 (100).

(4S,5S)-4,5-Bis(tert-butyldimethylsiloxymethyl)-2-hydroxymethyl-1,3-dioxolane **17**

The 2-propenyl-1,3-dioxolane **9** (0.15 g, 0.38 mmol) in methanol (15 cm^3) was ozonised at -78 °C over 1 h. The reaction mixture was then purged with O_2 and dimethylsulphide (1 cm^3) was added. The mixture was warmed to room temperature, concentrated under reduced pressure, the residue dissolved in dichloromethane (5 cm^3) and a solution of sodium borohydride (0.049 g, 1.31 mmol) in aqueous ethanol (3 cm^3) was added at 0 °C. The solution was stirred for 2.5 h at room temperature and acidified with aqueous hydrogen chloride (1 M). The aqueous layer extracted with dichloromethane (4 x 10 cm^3) and the organic extracts dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue using light petroleum: ethyl acetate (6:1) as eluent gave the *title compound* **17** (0.091 g, 61 %) (Found: M^+ + H, 393.2500. $C_{18}H_{41}O_5Si_2$ requires *M*, 393.2492); υ_{max}/cm^{-1} 3454, 1472, 1257, 1097, 838 and 778; δ_H (methanol-d_4) 0.48 (12 H, s, 4 x MeSi), 1.30 (18 H, s, 2 x Me_3CSi), 3.93 (2 H, d, *J* 4, 2-CH_2), 4.1 - 4.5 (6 H, m, 4-H, 5-H, 4-CH_2 and 5-CH_2) and 5.48 (1 H, t, *J* 4, 2-H); *m/z* (CI) 410 (M^+ + 18, 7 %) and 393 (M^+ + 1, 100).

*(4S,5S,1'E)-4,5-Bis(*tert*-butyldimethylsilyloxymethyl)-2-(2-ethoxycarbonylethenyl)-1,3-dioxolane* **18**

The 2-propenyl-1,3-dioxolane **9** (0.14 g, 0.34 mmol) in methanol (15 cm^3) was ozonised at -78 °C over 1 h. The reaction mixture was purged with O_2 and dimethylsulphide added, then warmed to room temperature and concentrated under reduced pressure. The residue was dissolved in dichloromethane (10 cm^3) and a solution of $Ph_3P{=}CHCO_2Et$ (0.49 g, 1.41 mmol) in dichloromethane (10 cm^3) was added. The reaction mixture was heated under reflux for 1 h, cooled to room temperature, triturated with petrol (6 x 10 cm^3), filtered and concentrated

under reduced pressure. Chromatography of the residue using light petroleum: ethyl acetate (6:1) as eluent gave the *title compound* **18** (0.144 g, 93 %), $[\alpha]_D$ + 3.9 (*c* 3.55 in MeOH) (Found: M^+ + H, 461.2754. $C_{22}H_{45}O_6Si_2$ requires *M*, 461.2755); υ_{max}/cm^{-1} 1729, 1472, 1364, 1257, 1097, 838 and 778; δ_H 0.06 (12 H, s, 4 x MeSi), 0.88 (18 H, s, 2 x Me_3CSi), 1.27 (3 H, t, *J* 7.5, CH_2CH_3), 3.62 - 4.12 (6 H, m, 4-H, 5-H, 4-CH_2 and 5-CH_2), 4.20 (2 H, q, *J* 7.5, CH_2CH_3), 5.53 (1 H, dd, *J* 5, 0.5, 2-H), 6.12 (1 H, dd, *J* 15, 0.5, 2'-H) and 6.77 (1 H, dd, *J* 15, 5, 1'-H); *m/z* (CI) 478 (M^+ + 18, 24 %), 461 (M^+ + 1, 78) and 460 (M^+, 2).

*(4S,5S)-4,5-Bis(*tert*-butyldimethylsilyloxymethyl)-2-ethenyl-1,3-dioxolane* **19**

The 2-propenyl-1,3-dioxolane **9** (0.092 g, 0.23 mmol) in methanol (10 cm^3) was ozonised at -78 °C over 1 h. The reaction mixture was purged with O_2, dimethylsulphide was added, and the mixture warmed to room temperature, azeotroped with benzene (3 x 15 cm^3) and concentrated under reduced pressure. The residue was dissolved in THF (5 cm^3) and added at 0 °C to a solution of $Ph_3P{=}CH_2$ in THF (5 cm^3) which had been prepared from methyltriphenylphosphonium bromide (0.18 g, 0.51 mmol) and butyllithium (1.% M; 0.35 cm^3, 0.52 mmol). The mixture was warmed to room temperature, stirred for 19 h and saturated aqueous ammonium chloride (3 cm^3) added. The mixture was washed with ethyl acetate (3 x 10 cm^3), water (3 x 5 cm^3), and brine (15 cm^3), and the aqueous washings extracted with ethyl acetate (2 x 10 cm^3). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue using light petroleum: ethyl acetate (7:1) as eluent gave the *title compound* **19** (0.014 g, 16 %); υ_{max}/cm^{-1} 1472, 1260, 1097, 1020, 838, 807 and 779; δ_H 0.07 (12 H, s, 4 x MeSi), 0.90 and 0.91 (each 9 H, s, Me_3CSi), 3.73 and 3.79 (each 2 H, dd, *J* 5.5, 4.5, 2 x *H*CH), 3.96 and 4.04 (each 1 H, m, 4-H, 5-H), 5.38 (2 H, m, 2'-H_2), 5.49 (1 H, m, 2-H) and 5.84 (1 H, m, 1'-H); *m/z* (CI) 406 (M^+ + 18, 34 %) and 389 (M^+ + 1, 13).

(1S,5R,7S)-4-(Ethoxycarbonylmethyl)-7-(hydroxymethyl)-3,6,8-trioxabicyclo[3.2.1]octane **20**

Tetrabutylammonium fluoride in THF (1 M; 0.1 cm^3, 0.1 mmol) was added to a solution of the dioxolane **18** (0.13 g, 0.29 mmol) in THF (10 cm^3). After 0.5 h, water (5 cm^3) was added and the mixture extracted with ethyl acetate (3 x 5 cm^3). The organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue using light petroleum: ethyl acetate (1:1) as eluent gave the *title compound* **20** (0.016 g, 24 %) (Found: M^+ + NH_4. 250.1292. $C_{10}H_{20}NO_6$ requires *M*, 250.1291); υ_{max}/cm^{-1} 3465, 1733, 1371, 1345, 1293, 1257, 1181, 1131, 1042, 979, 919 and 890; δ_H 1.25 (3 H, t, *J* 7, CH_2CH_3), 1.5 - 2.0 (1 H, br s, OH), 2.46 (1 H, dd, *J* 16, 6.5, 4-CH), 2.49 (1 H, dd, *J* 16, 7, 4-CH'), 3.62 (1 H, dd, *J* 11, 6, 7-CH), 3.64 (1 H, dd, *J* 11, 5, 7-CH'), 3.66 (1 H, dtd, *J* 12, 1.5, 0.5, 2-H), 3.97 (2 H, m, 2-H', 4-H), 4.15 (2 H, q, *J* 7, CH_2CH_3), 4.22 (1 H, q, *J* 1.5, 1-H), 4.33 (1 H, br t, *J* 5.5, 7-H) and 5.30 (1 H, d, *J* 1.5, 5-H); δ_C 14.2 36.4, 60.8, 64.1, 68.8, 73.4, 74.5, 76.6, 101.5 and 170.5; *m/z* (CI) 250 (M^+ + 18, 24 %) and 233 (100).

(4R,5R)-4,5-Bis(benzyloxymethyl)-2-(hydroxymethyl)-1,3-dioxolane **22**

The 1,3-dioxolane **14** (0.28 g, 0.78 mmol) in methanol (15 cm^3) was ozonised at -78 °C for 1 h. The reaction mixture was then purged with oxygen, dimethylsulphide (1 cm^3) was added, and the mixture warmed to room temperature and concentrated under reduced pressure. The residue was dissolved in dichloromethane (3 cm^3), the solution cooled to 0 °C, and sodium borohydride (0.25 g, 6.61 mmol) in wet ethanol (10 cm^3) was added. The reaction mixture was warmed to room temperature, stirred for 2.5 h and cooled to 0 °C. The mixture was acidified with aqueous hydrogen chloride (1 M) and water (5 cm^3) was added. The aqueous phase was extracted

with dichloromethane (4 x 10 cm^3) and the organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue using light petroleum: ethyl acetate (3:1) as eluent gave the *title compound* **22** (0.19 g, 69 %) (Found: $M^+ + NH_4$, 362.1969. $C_{20}H_{28}NO_5$ requires *M*, 362.1967); $[\alpha]_D$ +5.71 (*c* 4.9, $CHCl_3$); ν_{max}/cm^{-1} 3435, 3063, 3031, 1602 and 1070; δ_H 2.53 (1 H, br s, OH), 3.65 (6 H, m, 2-CH_2, 4-CH_2, and 5-CH_2), 4.15 (2 H, m, 4-H and 5-H), 4.57 (4 H, s, CH_2Ph), 5.22 (1 H, t, *J* 2.5, 2-H) and 7.25 (10 H, m, ArH); *m/z* (CI) 362 (M^+ + 18, 100 %).

*(4*R,*5*R,*2'*E*)-4,5-Bis(benzyloxymethyl)-2-(2-ethoxycarbonylethenyl)-1,3-dioxolane* **23**

The 2-propenyl-1,3-dioxolane **14** (1.0 g, 2.82 mmol) in dichloromethane (30 cm^3) was ozonised at - 78 °C for 1 h. The reaction mixture was then purged with O_2, dimethylsulphide (2 cm^3) was added, and the mixture was warmed to room temperature and concentrated under reduced pressure. The residue was dissolved in THF (20 cm^3), $Ph_3P{=}CHCO_2Et$ (2.0 g, 5.74 mmol) was added, and the mixture was heated under reflux for 15 h. After cooling to room temperature, the mixture was concentrated under reduced pressure, triturated with light petroleum (3 x 20 cm^3), filtered and concentrated under reduced pressure. Chromatography of the residue using cyclohexane: ethyl acetate (5:1) as eluent gave the *title compound* **23** (0.45 g, 39 %) (Found: C, 69.75; H, 7.0. $C_{24}H_{28}O_6$ requires C, 69.9; H, 6.85 %); $[\alpha]_D$ -3.6 (*c* 0.84, CH_3OH); ν_{max}/cm^{-1} ($CHBr_3$) 1716, 1640, 1270, 1089, 1069, 1043, 1028, 983 and 739; δ_H 1.28 (3 H, t, *J* 6, CH_2CH_3), 3.6 (4 H, m, 4-CH_2 and 5-CH_2), 4.15 (4 H, m, 4-H, 5-H and C$H_2$$CH_3$), 4.58 (4 H, s, C$H_2$Ph), 5.57 (1 H, d, *J* 5, 2-H), 6.15 (1 H, d, *J* 15, 2'-H), 6.81 (1 H, dd, *J* 15, 5, 1'-H) and 7.31 (10 H, m, ArH); *m/z* (CI) 430 (M^+ + 18, 100 %).

*(4*R,*5*R,*1'*Z*)-4,5-Bis(benzyloxymethyl)-2-(2-bromoethenyl)-1,3-dioxolane* **24**

The 2-propenyl-1,3-dioxolane **14** (0.17 g, 0.5 mmol) in dichloromethane (15 cm^3) was ozonised at -78 °C for 1 h. The reaction mixture was purged with oxygen, dimethylsulphide (1 cm^3) was added, and the mixture was warmed to room temperature and concentrated under reduced pressure. The residue was dissolved in THF (5 cm^3) and was added to a suspension of (bromomethyl)(triphenyl)phosphonium bromide (0.96 g, 2.2 mmol) and sodium bis(trimethylsilyl)amide in THF (1 M; 2 cm^3, 2 mmol) at -78 °C. The mixture was stirred for 0.5 h at -78 °C, warmed to room temperature and stirred for 24 h, then diluted with cyclohexane (20 cm^3) and water (10 cm^3), and extracted with ethyl acetate (3 x 10 cm^3). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue gave the *title compound* **24** (0.039 g, 19 %) (Found: $M^+ + NH_4$, 436.1121. $C_{21}H_{27}NO_4{}^{79}Br$ requires *M*, 436.1124); $[\alpha]_D$ -10.6 (*c* 2.26, CH_3OH); ν_{max}/cm^{-1} 3030, 1632, 1602 and 1101; δ_H 3.63 (4 H, m, 4-CH_2 and 5-CH_2), 4.13 (2 H, m, 4-H and 5-H), 4.57 and 4.60 (each 2 H, s, CH_2Ph), 5.88 (1 H, dd, *J* 7, 1, 2-H), 6.22 (1 H, t, *J* 7, 1'-H), 6.51 (1 H, dd, *J* 7, 1, 2'-H) and 7.32 (10 H, m, ArH); *m/z* (CI) 438, 436 (M^+ + 18, 75 and 100%).

*(4*R,*5*R*)-2-Acetyl-4,5-Bis(*tert*-butyldimethylsilyloxymethyl)-1,3-dioxolane* **25**

The 2-alkenyl-1,3-dioxolane **15** (4.85 g, 11.6 mmol) in methanol (28 cm^3) was ozonised at -78 °C for 1 h. The reaction mixture was then purged with O_2, dimethylsulphide (15 cm^3) was added, and the mixture warmed to room temperature and concentrated under reduced pressure. Chromatography of the residue using light petroleum: ethyl acetate (8:1) as eluent gave the *title compound* **25** (3.65 g, 78 %), $[\alpha]_D$ +0.6 (*c* 17.9, $CHCl_3$); ν_{max}/cm^{-1} 1735, 1473, 1257, 1101 and 837; δ_H 0.09 (12 H, s, 4 x MeSi), 0.92 (18 H, s, 2 x Me_3CSi), 2.25 (3 H, s, 2'-H_3), 3.8 (4 H, m, 4-CH_2 and 5-CH_2), 4.13 (2 H, m, 4-H and 5-H) and 5.10 (1 H, s, 2-H); δ_C -5.4,

18.3, 24.1, 25.9, 63.1, 63.3, 79.3, 79.6, 102.7 and 204.0; *m/z* (FAB) 403 (M^+ - 1, 13 %), 361 (10), 315 (92) and 275 (10); (CI) 394 (100).

On standing in air for 2 days, the ketone 25 gave the *carbonate* **27**, m.p. 92 - 93.2 °C (Found: $M^+ + NH_4$, 394.2453. $C_{17}H_{40}NO_5Si_2$ requires *M*, 394.2445); $[\alpha]_D$ -4.0 (*c* 30.1, $CHCl_3$); ν_{max}/cm^{-1} 1782, 1464, 1374, 1259, 1177, 1111, 1050, 839 and 780; δ_H 0.12 and 0.13 (each 6 H, s, Me_2Si), 0.93 (18 H, s, 2 x Me_3CSi), 3.77 (2 H, dd, *J* 12,2, 2 x *H*CH), 3.92 (2 H, dd, *J* 12, 3.5, 2 x HC*H*) and 4.64 (2 H, m, 4-H and 5-H); δ_C -5.5, 18.2, 25.7, 62.5, 77.7 and 154.8; *m/z* (CI) 394 (M^+ + 18, 100 %).

*(4R,5R,1'E)-4,5-Bis(*tert*-butyldimethylsilyloxymethyl)-2-(1-methyl-2-methoxycarbonylethenyl)-1,3-dioxolane* **26**

A solution of the 2-acetyl-1,3-dioxolane **25** (0.4 g, 0.98 mmol) and $Ph_3P{=}CHCO_2Me$ (2.36 g, 7.06 mmol) in dichloromethane (30 cm^3) was heated under reflux for 24 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure, triturated with light petroleum (3 x 10 cm^3), filtered and concentrated under reduced pressure. Chromatography of the residue using light petroleum: ethyl acetate (9:1) as eluent gave the *title compound* **26** (0.26 g, 58 %) (Found: $M^+ + NH_4$, 478.3019. $C_{22}H_{48}NO_6Si_2$ requires *M*, 478.3020); $[\alpha]_D$ +0.8° (*c* 29.1, $CHCl_3$); ν_{max}/cm^{-1} 1726, 1257, 1118, 838 and 778; δ_H 0.11 (12 H, s, 4 x MeSi), 0.92 and 0.93 (each 9 H, s, Me_3CSi), 2.16 (3 H, d, *J* 1.5, 1'-CH_3), 3.75 (3 H, s, CO_2Me), 3.8 (4 H, m, 4-CH_2 and 5-CH_2), 4.02 and 4.11 (each 1 H, m, 4-H, 5-H), 5.35 (1 H, s, 2-H) and 6.05 (1 H, br s, 2'-H); δ_C -5.4, 13.0, 18.3, 25.9, 51.2, 63.6, 63.7, 79.1, 79.3 105.6, 118.5, 153.2 and 166.7; *m/z* (CI) 478 (M^+ + 18, 100 %).

(4R,5R)-4,5-Bis(benzoyloxymethyl)-2-tributylstannyl-1,3-dioxolane **31**

Toluene *p*-sulfonic acid (30 mg) and (diethoxymethyl)tributylstannane **30**[8] (1.2 g, 3.05 mmol) were added to the diol **29** (500 mg, 1.52 mmol) in benzene (50 cm^3) and the mixture heated under reflux with azeotropic removal of ethanol. Fresh benzene was added over 4 h (6 x 50 cm^3) and removed by distillation using a Dean-Stark apparatus. On cooling, the reaction mixture was filtered through a pad of potassium carbonate, and the filtrate concentrated under reduced pressure. Chromatography of the residue using light petroleum: ether (6:1) as eluent gave the *title compound* **31** (0.77 g, 80 %), $[\alpha]_D$ + 8.6 (*c* 0.55, $CHCl_3$) (Found: M^+ + H, 633.2235. $C_{31}H_{45}O_6{}^{120}Sn$ requires *M*, 633.2238; ν_{max}/cm^{-1} 1817, 1725, 1603, 1452, 1271, 1114, 1069 and 711; δ_H 1.05 (15 H, m, 3 x CH_3CH_2), 1.20 - 1.70 (12 H, m, 6 x CH_2), 4.13 and 4.3 (each 1 H, m, 4-H, 5-H), 4.4 - 4.65 (4 H, m, 4-CH_2 and 5-CH_2), 5.42 (1 H, s, 2-H), 7.43 - 7.65 (6 H, m, ArH) and 8.10 (4 H, m, ArH); δ_C 9.0, 13.6, 27.3, 29.0, 63.5, 64.4, 106.6, 128.4, 129.8, 133.2 and 166.3; *m/z* (CI) 650 (M^+ + 18, 50 %), 633 (M^+ + 1, 20) and 575 (10).

(4R,5R)-4,5-Bis(hydroxymethyl)-2-tributylstannyl-1,3-dioxolane **32**

Lithium hydroxide (2.0 g, 85.31 mmol) was added to a solution of the benzoate **31** (5.4 g, 8.53 mmol) in methanol (30 cm^3). After 1 h, the mixture was concentrated under reduced pressure and the residue dissolved in ethyl acetate. After extraction with pH 7 buffer and brine, the aqueous layers were extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue using light petroleum: ether 3 : 1) as eluent gave the *title compound* **32** (3.5 g, 98 %), $[\alpha]_D$ +2.7 (*c* 1.62, $CHCl_3$) (Found: M^+ - C_4H_9, 367.0939. $C_{13}H_{27}O_4{}^{120}Sn$ requires *M*, 367.0931); ν_{max}/cm^{-1} 3375, 1464,

1377, 1051 and 933; δ_H 0.80 - 1.10 (15 H, m, 3 x CH_3CH_2), 1.23 - 1.71 (12 H, m, 6 x CH_2), 2.50 (2 H, br, 2 x OH), 3.55 - 3.85 (6 H, m, 4-H, 5-H, 4-CH_2 and 5-CH_2), and 5.25 (1 H, s, 2-H); δ 9.4, 14.2, 27.8, 29.4, 62.6, 63.3, 78.9, 80.6 and 106.7; *m/z* (CI) 425 (M^+ + 1, 3 %) and 367 (10).

*(4*R,*5*R*)-4,5-Bis(*tert*-butyldimethylsilyloxymethyl)-2-tributylstannyl-1,3-dioxolane* **33**

Imidazole (2.6 g, 37.74 mmol) and *tert*-butyldimethylsilyl chloride (4.24 g, 28.30 mmol) were added to a solution of the diol **32** (4 g, 9.43 mmol) in dichloromethane (40 cm^3). After 16 h, the mixture was concentrated under reduced pressure and the residue dissolved in ether. The ethereal solution was washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue using 1 % ether in light petroleum as eluent gave the *title compound* **33** (5.4 g, 88 %), $[\alpha]_D$ +3.9 (*c* 2.52, $CHCl_3$) (Found: M^+ + H, 653.3372. $C_{29}H_{65}O_4Si_2{}^{120}Sn$ requires *M*, 653.3365); ν_{max}/cm^{-1} 1463, 1255, 1142, 1099, 1035, 838 and 778; δ_H 0.06 (6 H, s, Me_2Si), 0.07 (6 H, s, Me_2Si), 0.80 - 1.00 (33 H, 3 x CH_3CH_2 and 2 x Me_3CSi), 1.22 - 1.71 (12 H, m, 6 x CH_2), 3.26 - 3.80 (6 H, m, 4-H, 5-H, 4-CH_2 and 5-CH_2) and 5.27 (1 H, s, 2-H); δ_C -4.8, 9.3, 14.2, 18.9, 26.4, 27.8, 29.5, 64.0, 65.0, 79.5, 80.6 and 106.8; *m/z* (CI) 653 (M^+ + 1, 10 %).

Synthesis of 2-(1-hydroxyalkyl)-1,3-dioxolanes from the 2-tributylstannyl-1,3-dioxolane **33**

*(4*R,*5*R*)-4,5-Bis(*tert*-butyldimethylsilyloxymethyl)-2-(1-hydroxy-2-methylpropyl)-1,3-dioxolane* **34**

Butyllithium in hexane (1.6 M; 0.21 cm^3, 0.34 mmol) was added to a solution of the stannane **33** (200 mg, 0.31 mmol) in THF (2 cm^3) at -78 °C. After 20 min, 2-methylpropanal (0.03 cm^3, 0.4 mmol) was added and the reaction mixture warmed to room temperature over 30 min. The reaction mixture was then diluted with ether and washed with water and brine, dried (Na_2SO_4), and concentrated under reduced pressure. Chromatography using light petroleum: ether (5:1) as eluent gave the *title compound* **34** (77 mg, 50 %) $[\alpha]_D$ +0.7 (*c* 1.8, $CHCl_3$) (Found: M^+ + H, 435.2960. $C_{21}H_{47}O_5Si_2$ requires *M*, 435.2962); ν_{max}/cm^{-1} 3507, 1471, 1256, 1139, 1097, 837 and 777; δ_H 0.15 (12 H, s, 2 x Me_2Si), 0.90 - 1.15 (24 H, m, 2 x Me_3CSi and Me_2CH), 1.85 (1 H, m, 2'-H), 2.5 (0.5 H, d, *J* 5, OH), 2.55 (0.5 H, d, *J* 3, OH), 3.32 (1 H, m, 1'-H), 3.80 (4 H, m, 4-CH_2 and 5-CH_2), 4.08 (2 H, m, 4-H and 5-H) and 5.17 (1 H, m, 2-H); δ_C -5.0, 18.2, 18.3, 18.4, 18.5, 18.8, 18.9, 25.8, 25.9, 30.1, 30.5, 63.4, 63.5, 63.7, 63.8, 78.4, 78.9, 78.9, 104.2 and 104.2; *m/z* (CI) 452 (M^+ + 18, 100 %) and 435 (M^+ + 1, 90).

The following compounds were obtained following this procedure:

*(4*R,*5*R*)-4,5-Bis(*tert*-butyldimethylsilyloxymethyl)-2-(hydroxyphenylmethyl)-1,3-dioxolane* **35** (56 mg, 68 %), $[\alpha]_D$ -3.0 (*c* 0.70, $CHCl_3$) (Found: M^+ + H, 469.2812. $C_{24}H_{45}O_5Si_2$ requires *M*, 469, 2806); ν_{max}/cm^{-1} 3456, 1390, 1362, 1472, 1256, 1142, 1095, 837 and 778; δ_H 0.10 (12 H, 5 x s, 2 x Me_2Si), 0.91 and 1.0 (each 9 H, s, 2 x Me_3CSi), 3.30 (0.5 H, d, *J* 2.5, OH), 3.40 (0.5 H, d, *J* 5.5, OH), 3.72 - 4.24 (6 H, m, 4-H, 5-H, 4-CH_2 and 5-CH_2), 4.74 (1 H, m, 1'-H), 5.21 and 5.25 (each 0.5 H, d, *J* 3, 2-H) and 7.4 (5 H, m, ArH); δ_C -5.0, 18.7, 18.9, 26.4, 26.3, 63.9, 64.1, 64.2, 78.7, 79.8, 80.0, 106.8, 127.0, 127.3, 128.5, 128.7, 139.4 and 140.0; *m/z* (CI) 486 (M^+ + 18, 100 %) and 469 (M^+ + 1, 50).

*(4*R,*5*R*)-4,5-Bis(*tert*-butyldimethylsilyloxymethyl)-2-(1-hydroxyprop-2-enyl)-1,3-dioxolane* **36** (82 mg, 64 %), $[\alpha]_D$ +8.6 (*c* 0.86, $CHCl_3$) (Found: M^+ + H, 419.2648. $C_{20}H_{43}O_5Si_2$ requires *M*, 419.2649); ν_{max}/cm^{-1} 3482, 1472, 1256, 1139, 1098, 1004, 837 and 778; δ_H 0.05 and 0.06 (each 3 H, s, MeSi), 0.09 (6 H, s, 2 x MeSi), 0.89 and 0.91 (each 9 H, s, Me_3CSi), 2.82 (0.5 H, d, *J* 7, OH), 2.87 (0.5 H, d, *J* 3, OH), 3.70 - 4.20 (7 H , m, 4-H, 5-H, 4-CH_2, 5-CH_2 and 1'-H), 5.05 and 5.07 (each 0.5 H, d, *J* 5, 2-H), 5.3 (2 H, m, 3'-H_2)

and 5.90 (1 H, m, 2'-H); δ_C -5.0, 18.8, 18.9, 26.3, 26.4, 63.8, 64.1, 74.1, 79.6, 79.8, 105.7, 106.0, 117.2, 117.7, 135.8 and 136.4; *m/z* (CI) 436 (M^+ + 18, 95 %) and 419 (M^+ + 1, 100).

*(4R,5R)-4,5-Bis(*tert*-butyldimethylsilyloxymethyl)-2-[(methoxycarbonyl)(hydroxy)methyl]-1,3-dioxolane* **37** (80 mg, 45 %), $[\alpha]_D$ +1.2 (*c* 0.58, $CHCl_3$) (Found: M^+ + H, 451.2547. $C_{20}H_{43}O_7Si_2$ requires *M*, 451.2547); ν_{max}/cm^{-1} 3508, 1780, 1755, 1256, 1150, 1096, 837 and 778; δ_H 0.10 (12 H, m, 2 x Me_2Si), 0.95 (18 H, s, 2 x Me_3CSi), 3.34 (0.5 H, d, J 6, OH), 3.70 - 4.40 (7.5 H, m, OH, 4-H, 5-H, 4-CH_2, 5-CH_2 and 1'-H), 3.81 and 3.82 (each 1.5 H, s, OMe) and 5.46 and 5.48 (each 0.5 H, d, *J* 1.5, 2-H); δ_C -5.0, 18.7, 18.9, 26.3, 26.4, 52.8, 52.9, 63.6, 64.0, 72.6, 73.5, 79.7, 79.9, 104.1, 171.4 and 171.9; *m/z* (CI) 468 (M^+ + 18, 100 %) and 451 (M^+ + 1, 75).

*(4R,5R)-4,5-Bis(*tert*-butyldimethylsilyloxymethyl)-2-(2-methyl-1-oxopropyl)-1,3-dioxolane* **38**

N-Methylmorpholine-*N*-oxide (22 mg, 0.215 mmol), TPAP (3 mg), and 4Å sieves were added to a solution of the alcohol **34** (60 mg, 0.144 mmol) in dichloromethane (2 cm^3). After 1 h, the reaction mixture was decanted from the sieves, and hexane (1 cm^3) was added. The solution was filtered through a pad of silica and the filtrate concentrated under reduced pressure to afford the *title compound* **38** (56 mg, 95 %), $[\alpha]_D$ +0.4 (*c* 1.04, $CHCl_3$) (Found: M^+ + H, 433.2808. $C_{21}H_{45}O_5Si_2$ requires *M*, 433.2806); ν_{max}/cm^{-1} 1731, 1472, 1257, 1142, 1104, 1005, 838 and 778; δ_H 0.10 (12 H, s, 2 x Me_2Si), 0.95 (18 H, s, 2 x Me_3CSi), 1.15 (6 H, d, *J* 7, Me_2CH), 3.10 (1 H, sep, *J* 7, Me_2CH), 3.82 (4 H, m, 4-CH_2 and 5-CH_2), 4.10 (2 H, m, 4-H and 5-H) and 5.25 (1 H, s, 2-H); δ_C -5.4, 18.3, 25.8, 29.7, 35.3, 63.3, 79.3, 102.1 and 209.1; *m/z* (CI) 450 (M^+ + 18, 45 %) and 433 (M^+ + 1, 100).

*(4R,5R)-4,5-Bis(*tert*-butyldimethylsilyloxymethyl)-2-benzoyl-1,3-dioxolane* **39**

Following the procedure outlined for the synthesis of the ketone **38**, the alcohol **35** was oxidized to the *title compound* **39** (20 mg, 100 %), (Found: M^+ + H, 467.2654. $C_{24}H_{43}O_5Si_2$ requires *M*, 467.2649); ν_{max}/cm^{-1} 1705, 1255, 1142, 1097, 837 and 779; δ_H -0.01 and 0.01 (each 3 H, s, MeSi, 0.10 (6 H, s, Me_2Si), 0.85 and 0.92 (9 H, s, Me_3CSi), 3.71 - 4.03 (4 H, m, 4-CH_2 and 5-CH_2), 4.23 (2 H, m, 4-H and 5-H), 5.98 (1 H, s, 2-H), 7.5 (3 H, m, ArH) and 8.05 (2 H, m, ArH); δ_C -5.0, 18.8, 26.4, 63.8, 64.0, 79.7, 80.2, 101.9, 129.0, 129.9, 134.1 and 194.0; *m/z* (CI) 484 (M^+ + 18, 75 %) and 467 (M^+ + 1, 50).

(4S,5S)-4,5-Bis(ethoxycarbonyl)-2-(3-pyridyl)-1,3-dioxolane **41**

A mixture of the diethylacetal **40**[9] (0.49 g, 2.72 mmol), (*S,S*)-diethyl tartrate (1.16 g, 56.3 mmol) and pyridinium toluene *p*-sulfonate (0.02 g, 0.08 mmol) in benzene (75 cm^3) was heated under reflux and the solvent and ethanol allowed to distil off slowly. After cooling and concentration under reduced pressure, chromatography of the residue using light petroleum: ethyl acetate (2:1) as eluent gave the *title compound* **41** (0.43 g, 53 %) (Found: M^+ + H, 296.1137. $C_{14}H_{18}NO_6$ requires *M*, 296.1134); $[\alpha]_D$ +13.44 (*c* 2.24, $CHCl_3$); ν_{max}/cm^{-1} ($CHBr_3$) 1743, 1584, 1550, 1223, 1096, 1027, and 737; δ_H 1.30 and 1.36 (each 3 H, t, *J* 7.5, CH_2CH_3), 4.28 and 4.34 (each 2 H, q, *J* 7.5, CH_2CH_3), 4.86 and 4.97 (each 1 H, d, *J* 4, 4-H, 5-H), 6.22 (1 H, s, 2-H), 7.35 (1 H, dd, *J* 8, 5, 5'-H), 7.97 (1 H, ddd, *J* 8, 2, 1.5, 6'-H), 8.66 (1 H, br d, *J* 5, 4'-H) and 8.78 (1 H, br s, 2'-H); δ_C 14.2, 15.0, 61.3, 61.8, 62.2, 72.1, 74.7, 99.1, 123.6, 135.8, 147.6, 148.9, 168.9 and 171.0; *m/z* (CI) 342 (M^+ + 18, 100 %).

(4R,5R)-4,5-Bis(hydroxymethyl)-2-(3-pyridyl)-1,3-dioxolane **42**

The diester **41** (0.14 g, 0.48 mmol) in ethanol (10 cm^3) was added to a solution of sodium borohydride (0.18 g, 4.76 mmol) in ethanol (5 cm^3) at 0 °C and the reaction mixture was warmed to room temperature, stirred for 2 h, and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate as eluent gave the *title compound* **42** (0.09 g, 87 %) as a white powder, m.p. 77.1 -78.5 °C, $[\alpha]_D$ -29.2 (*c* 2.5, CH_3OH) (Found: C, 56.8; H, 6.1; N, 6.5. $C_{10}H_{13}NO_4$ requires C, 56.85; H, 6.2; N, 6.65 %); ν_{max}/cm^{-1} 3341, 1602, 1438, 1083, 1029, 808 and 713; δ_H (methanol-d_4) 3.86 (4 H, m, 4-CH_2 and 5-CH_2), 4.2 (2 H, m, 4-H and 5-H), 6.12 (1 H, s, 2-H), 7.55 (1 H, dd, *J* 7.5, 5, 5'-H), 8.07 (1 H, ddd, *J* 7.5, 2, 1.5, 6'-H), 8.64 (1 H, dd, *J* 5, 1.5, 4'-H) and 8.75 (1 H, d, *J* 2, 2'-H); δ_C (methanol-d_4) 63.0, 63.2, 80.5, 81.0, 103.0, 125.1, 136.0, 136.9, 148.9 and 150.8; *m/z* (CI) 212 (M^+ + 1, 92 %) and 180 (6).

1-Benzyl-5-(hydroxymethyl)-2-pyridone **45**

Potassium carbonate (0.87 g, 6.29 mmol) and thionyl chloride (0.5 cm^3, 6.85 mmol) were added to a solution of the acid **43**[10] (0.48 g, 1.97 mmol) in benzene (50 cm^3) and the mixture was heated to 50 °C for 2.5 h. After cooling, the mixture was concentrated under reduced pressure to yield the acid chloride **44**; ν_{max}/cm^{-1} 1745, 1667 and 1610; δ_H 5.19 (2 H, s, 1-CH_2), 6.60 (1 H, d, *J* 9, 3-H), 7.37 (5 H, m, ArH), 7.84 (1 H, dd, *J* 9, 2.5, 4-H) and 8.38 (1 H, d, *J* 2.5, 6-H). Sodium borohydride (0.49 g, 13 mmol) was added to this acid chloride in THF (20 cm^3) at 0 °C. The reaction mixture was stirred for 3 h at room temperature, then cooled to 0 °C and wet methanol was added dropwise. The solution was concentrated under reduced pressure, diluted with ethyl acetate (100 cm^3) and washed with water (2 x 25 cm^3). The aqueous layer was extracted with ethyl acetate (3 x 35 cm^3) and the organic extracts dried (Na_2SO_4) and concentrated under reduced pressure to yield the *title compound* **45** (0.11 g, 29 %), m.p. 109-111 °C (Found: C, 72.2; H, 6.0; N, 6.75. $C_{13}H_{13}NO_2$ requires C, 72.55; H, 6.1; N. 6.55 %; Found: M^+ + H, 216.1014. $C_{12}H_{14}NO_2$ requires *M*, 216.1024); ν_{max}/cm^{-1} 3324, 1664, 1583 and 1542; δ_H 2.62 (1 H, br s, OH), 4.45 (2 H, s, 5-CH_2), 5.15 (2 H, s, 1-CH_2), 6.69 (1 H, d, *J* 9, 3-H), 7.35 (7 H, m, 4-H, 6-H and ArH); δ_C 52.3, 61.8, 112.0, 120.9, 128.2, 129.0, 135.4, 136.1, 140.1 and 162.4; *m/z* (CI) 233 (M^+ + 18, 8 %) and 216 (100).

1-Benzyl-5-formyl-2-pyridone **46**

Manganese dioxide (7.46 g, 85.7 mmol) was added to a solution of the alcohol **45** (1.66 g, 7.71 mmol) in dichloromethane (80 cm^3). After stirring at room temperature for 5 h, the mixture was filtered and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate as eluent gave the *title compound* **46** (0.66 g, 40 %), m.p. 93 - 94 °C (Found: M^+ + NH_4, 231.1132. $C_{13}H_{15}N_2O_2$ requires *M*, 231.1133); ν_{max}/cm^{-1} 3438, 3030, 1660, 1616, 1547, 1497, 1449, 1388, 1262, 1229, 1133 and 839; δ_H 5.22 (2 H, s, 1-CH_2), 6.69 (1 H, d, *J* 9, 3-H), 7.35 - 7.45 (5 H, m, ArH), 7.84 (1 H, dd, *J* 9, 2.5, 4-H), 7.92 (1 H, d, *J* 2.5, 6-H) and 9.60 (1 H, s, CHO); δ_C 52.6, 118.5, 121.2, 128.4, 128.7, 129.3, 135.0, 135.8, 146.1, 162.6 and 186.0; *m/z* (CI) 231 (M^+ + 18, 30 %) and 214 (100).

(4'S,5'S)-1-Benzyl-5-[4,5-bis(ethoxycarbonyl)-1,3-dioxolan-2-yl]-2-pyridone **47**

The aldehyde **46** (0.30 g, 1.42 mmol), (*S,S*)-diethyl tartrate (0.44 g, 2.13 mmol) and toluene *p*-sulfonic acid (0.3 g, 1.58 mmol) in benzene (50 cm^3) were heated under reflux using a Dean and Stark trap for 24 h. The mixture was cooled to room temperature and concentrated under reduced pressure. Reverse phase HPLC using

methanol: water (4:1; retention time 5.59 min) as eluent gave the *title compound* **47** (0.022 g, 4 %) as a white solid (Found: M^+, 401.4141. $C_{21}H_{23}NO_7$ requires *M*, 401.4152); ν_{max}/cm^{-1} 1750, 1673, 1618, 1546, 1377, 1220, 1106, 1028, 957 and 837; δ_H 1.35 and 1.37 (each 3 H, t, *J* 7, CH_2CH_3), 4.32 (4 H, m, 2 x CH_2CH_3), 4.79 and 4.91 (each H, d, *J* 3.5, 4'-H, 5'-H), 5.14 and 5.22 (each 1 H, d, *J* 14, 1-CH), 5.90 (1 H, s, 2'-H), 6.72 (1 H, d, *J* 9, 3-H), 7.37 (5 H, m, ArH), 7.57 (1 H, d, *J* 2.5, 6-H) and 7.64 (1 H, dd, *J* 9, 2.5, 4-H); *m/z* (EI) 401 (M^+, 75 %) and 328 (40).

ACKNOWLEDGEMENTS

We thank the EPSRC and Glaxo Wellcome Research for CASE Studentships (to P. E. M. and B. J. M.) and Dr. P. Woodward of Glaxo Wellcome for many helpful discussions.

REFERENCES

1 De Mesmaeker, A.; Haner, R.; Martin, P.; Moser, H. E., *Acc. Chem. Res.*, **1995**, *28*, 366-374; Uhlmann, E.; Peyman, A., *Chem. Rev.*, **1990**, *90*, 543-584; Varma, R S., *Synlett*, **1993**, 621-637.

2 Butterfield, K.; Thomas, E. J., *J. Chem. Soc., Perkin Trans. I*, **1998**, submitted for publication; Mellor, B. J.; Thomas, E. J., *J. Chem. Soc., Perkin Trans. I*, **1998**, submitted for publication; Butterfield, K.; Thomas, E. J., *Synlett*, **1993**, 411-412.

3 Branalt J.; Kvarnstrom, I.; Classon, B.; Samuelsson, B., *J. Org. Chem.*, **1996**, *61*, 3599-3603; Xiang, Y.; Teng, Q.; Chu, C. K., *Tetrahedron Lett.*, **1995**, *36*, 3781-3784.

4 Mori, A.; Arai, I.; Yamamoto, H.; Nakai, H.; Arai, Y., *Tetrahedron*, **1986**, *42*, 6447-6458; Heitz, M. P.; Gellibert, F.; Mioskowski, C., *Tetrahedron Lett.*, **1986**, *27*, 3859-3860.

5 VanAllan, J. A., *Org. Synth.*, **1952**, *32*, 5-6; Newman-Evans, R. H; Simon, R. J.; Carpenter, B. K., *J. Org. Chem.*, **1990**, *55*, 695-711.

6 Takano, S.; Satoh, S.; Ogasawara, K., *Heterocycles*, **1990**, *30*, 583-605.

7 Wenger, R. M., *Helv.*, **1983**, *66*, 2308-2321.

8 Shiner, C. S.; Tsunoda, T.; Goodman, B. A.; Ingham, S.; Lee, S-h.; Vorndam, P. E., *J. Am. Chem. Soc.*, **1989**, *111*, 1381-1392.

9 Eriguchi, A.; Takegoshi, T., *Chem. Pharm. Bull.*, **1982**, 428-439.

10 Buurman, D. J.; van der Plas, H. C., *J. Het. Chem.*, **1986**, *23*, 1015-1018; Anderson, A. G.; Berkelhammer, G., *J. Am. Chem. Soc.*, **1958**, *80*, 992-999.

11 Trummlitz, G.; Moffatt, J. C., *J. Org. Chem.*, **1973**, *38*, 1841-1845; Wnuk, S. F., *Tetrahedron*, **1993**, *49*, 9877-9936; Borthwick, A. D.; Biggadike, K., *Tetrahedron*, **1992**, *48*, 571-623.