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Herboxidiene: Determination of Absolute Configuration by Degradation and Synthetic Studies

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Abstract: Degradation of the novel polyketide herbicide herboxidiene leads to useful fragments for further analogue synthesis and also enabled determination of the absolute configuration of the natural product *via* asymmetric synthesis of the respective fragments.

The isolation and structure elucidation of a secondary metabolite produced by *Streptomyces* strain A7847 by Isacc *et al.* revealed a novel polyketide natural product.[1] This compound displays phytotoxicity (>90%) against several important biannual weeds including oilseed rape, wild buckwheat and morning glory at relatively low rates of application (35g acre $^{-1}$) without causing damage to wheat. Structurally interesting features of the natural product are the tetrahydropyran acetic acid moiety and the conjugated diene system. On the basis of the structural and biological properties, the compound was named herboxidiene, **1**.

Although extensive NMR studies enabled assignment of the relative stereochemistry at most of the stereogenic centres,[1] the configuration at carbons 12, 16, 17 and 18 have hitherto remained unknown. The first stereoselective synthesis of the herboxidiene skeleton has recently been published,[2] but comparison of synthetic material with the natural product showed that the compounds were diastereoisomers. We were also intrigued by the relatively simple structure of this molecule which suggested it would be a good target for analogue synthesis, and thus a synthetic program was initiated. In order to aid our, and other,[2,3] synthetic programs, the relative and absolute configuration of the molecule was clearly required. In this paper, we reveal the absolute configuration of herboxidiene which has been obtained by selective degradation of the natural product and asymmetric synthesis of the respective fragments.

Herboxidiene was isolated independently by Le-Van *et al.*, and the relative stereochemistry could be ascertained by X-ray analysis of crystals obtained by controlled crystallisation from methylene chloride/methanol.[4,5] The relative stereochemistry is shown in Figure 1.

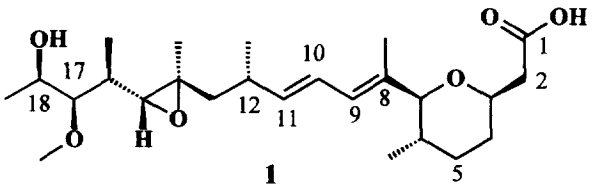

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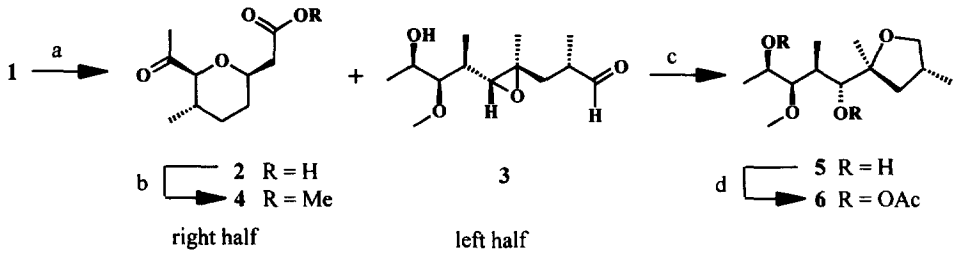
Figure 1. Relative stereochemistry of herboxidiene (**1**).

To determine the absolute stereochemistry, it was required that the natural product be degraded into fragments, which could then in turn be separately prepared by asymmetric synthesis for optical rotation comparison. Furthermore, the cleavage of herboxidiene should be carried out in such a manner that the fragments could be used for the preparation of semi-synthetic analogues.

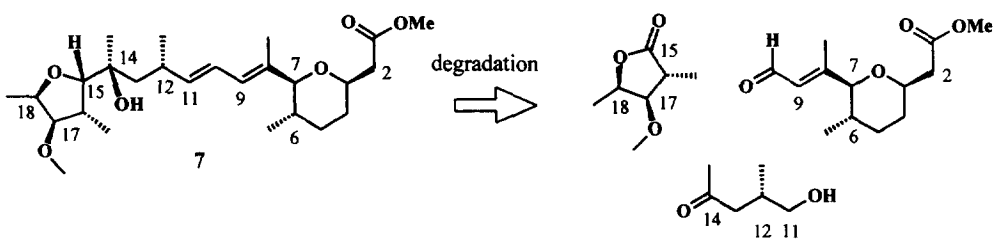
Using a modified procedure to that previously reported,[1] ozonolysis of herboxidiene (Scheme 1) led to the tetrahydropyran acetic acid **2** and the very unstable aldehyde **3**. The acid was converted to the methyl ester **4** to enable easier purification. Reduction of **3** also led to a very unstable primary alcohol which cyclised *in situ* to the tetrahydrofuran derivative **5**, the structure of which was confirmed by conversion to the diacetate **6**.[6] Although this cleavage procedure gives rapid access to the right half of the molecule (albeit with loss of the stereochemical information of the double bonds) the left hand portion of the molecule (i.e. **5**) is of little use for preparation of semi-synthetic derivatives.



Scheme 1.

Reagents and Conditions. a) O_3 / CH_2Cl_2 , -78^{0}C then add dimethyl sulfide, -78^{0}C to r.t. b) MeOH/HCl, reflux. c) $NaBH_4$/MeOH/THF, r.t. d) Ac_2O/Pyr, r.t.

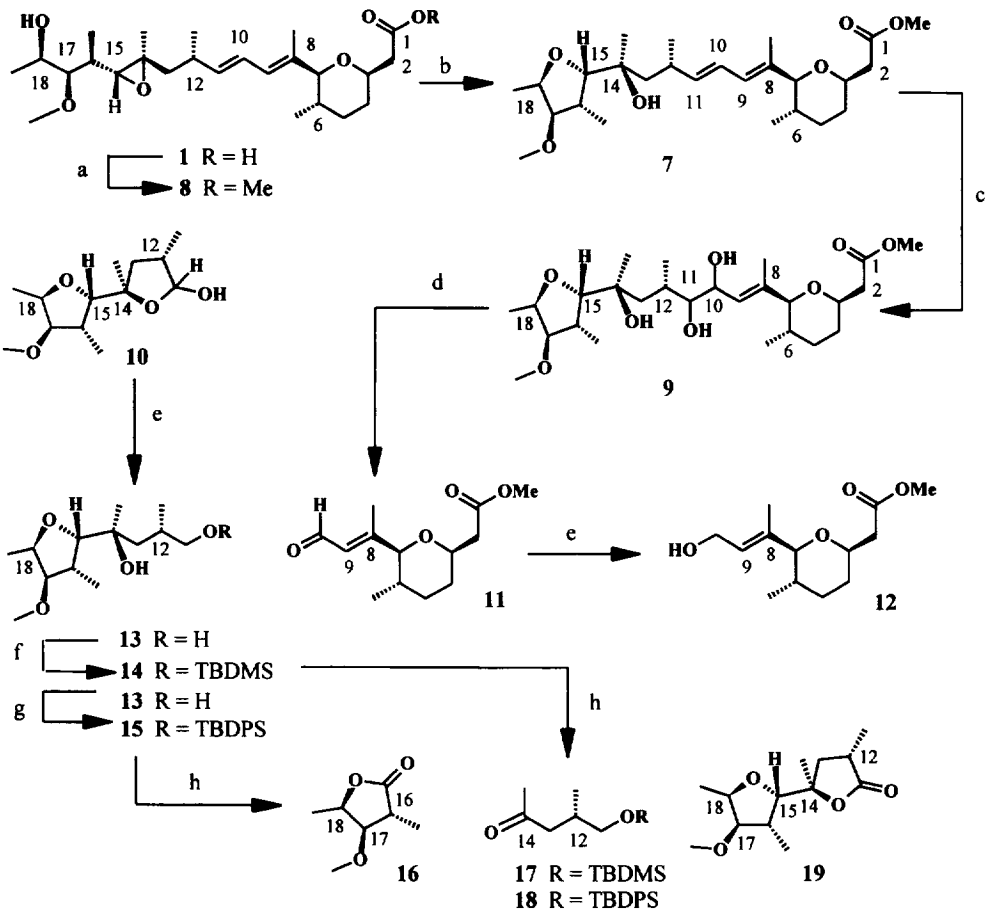
An alternative procedure was therefore investigated which envisaged (Scheme 2) cleavage of the C10-C11 and C14-C15 bonds in the readily available tetrahydrofuran derivative **7**.[7]



Scheme 2.

As shown in Scheme 3, herboxidiene was first esterified with potassium carbonate and dimethyl sulfate in DMF to yield the known[1] methyl ester **8** in excellent yield. It has been reported[1] that treatment of herboxidiene methyl ester with NaOMe in MeOH at 60^{0}C yields the tetrahydrofuran derivative **7** which arises by intramolecular opening of the oxirane by the 18-hydroxyl functionality. Alternatively, this compound is also readily obtained by treatment of the methyl ester with anhydrous MeOH/HCl.[8,9] The tetrahydropyran **7** was then regioselectively[10] dihydroxylated at the least hindered C10-C11 double bond and the crude mixture of diol diastereoisomers **9** then cleaved to the α,β-unsaturated aldehyde **11** and the tetrahydropyran aldehyde **10** (masked as a hemi-acetal) with periodate. Subsequent reduction proceeded without complication to yield the corresponding alcohols **12** and **13**. Inspection of **13** reveals a tertiary alcohol functionality at C14 (herboxidiene numbering). Such tetrahydrofuran methanol derivatives can be oxidatively cleaved by pyridinium chlorochromate (PCC) in refluxing methylene chloride.[11] In order to apply such chemistry in this case, **13** was

selectively protected at the primary alcohol function as a tert.-butyldimethylsilyl (TBDMS) ether and, following oxidation, the required cleavage products **16** and **17** were obtained in good yields together with small amounts (7%) of the bicyclic lactone **19**.[12,13] The lactone **19** arises by partial deprotection of the alcohol function under the slightly acidic reaction conditions and subsequent transformation *via* the hemi-acetal **10** to the oxidatively stable **19**. Protection as the more acid stable tert.-butyldiphenylsilyl (TBDPS) ether[14] improved the yields by completely suppressing formation of **19**.

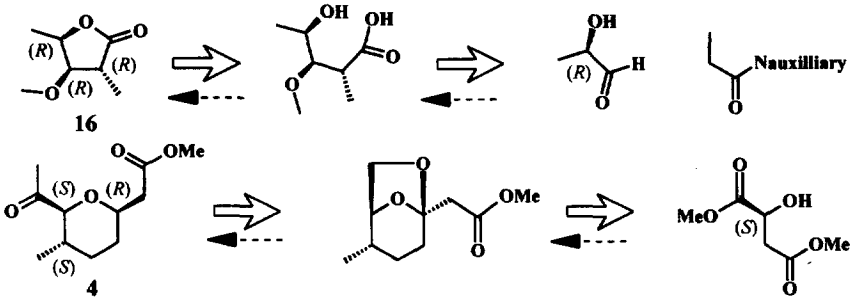


Scheme 3.

Reagents and Conditions. a) K_2CO_3/DMF/ $(MeO)_2SO_2$, 90°C. b) HCl/MeOH, 0°C. c) N-methyl morpholin oxide (NMO)/OsO_4 (5%)/acetone/H_2O, r.t. d) $NaIO_4$/H_2O/THF, r.t. e) $NaBH_4$/THF/MeOH, 0°C to r.t. f) TBDMSCl/imidazole/DMAP/DMF, 0°C to r.t. g) As e), but use TBDPSCl. h) PCC/4A° M. Sieves/CH_2Cl_2, reflux.

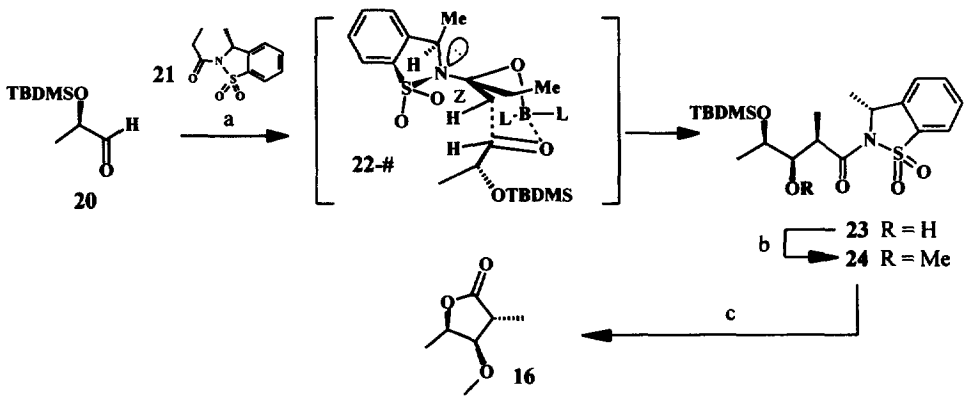
With the appropriate degradation products **4** and **16** in hand, asymmetric synthesis was required to determine the absolute configuration. As shown in Scheme 4, retrosynthetic analysis of the lactone showed that the *R,R,R*-configuration would be available *via* asymmetric aldol reaction of a protected 2-(*R*)-hydroxy propionaldehyde with a chiral propionyl enolate. The approach to the tetrahydropyran fragment **4** with *R,S,S*-configuration would embrace as its key step a process developed by Kotsuki *et al.* for the stereoselective

reduction of bicyclic ketals with inversion of configuration.[15] The bicyclic ketal required for the reduction would in turn be synthesised from (*S*)-dimethyl malate.



Scheme 4.

Beginning with the lactone **16** (Scheme 5), treatment of the known chiral aldehyde **20**[16] with the boron enolate of the saccharin derived propionyl sultam **21** at -5°C, according to the procedure of Walther,[17] led after work up and purification to the aldol product **23** in good yield and with greater than 95% 2,3-*syn*, 3,4-*syn* selectivity.[18] A single recrystallisation gave the pure syn-syn diastereoisomer **23**.[19] The stereochemistry reflects an electrophilic attack to the more hindered π-face of the (Z)-"enolate". This is rationalised by the transition state **22-#** in which the boron atom is fully coordinated (and thus incapable of chelation with an SO_2 oxygen atom) with the "enolate" adopting an electrostatically favoured N-SO_2/C-OML_n *s-trans* configuration.[20] Alkylation to **24** was accomplished in quantitative yield by the method of Evans,[21] and deprotection by treatment of the latter with 4% HF in acetonitrile resulted in direct cyclisation to the required lactone **16**.

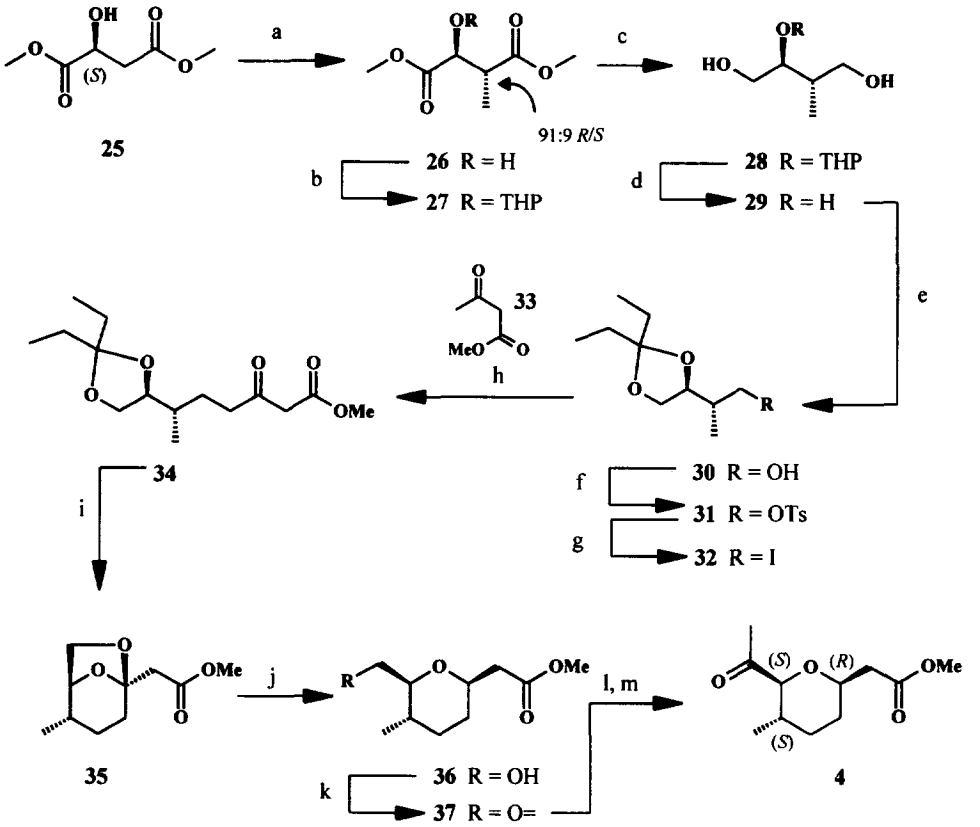


Scheme 5.

Reagents and Conditions. a) $Et_2B(OTf)/(^iPr)_2NEt$/**21**/CH_2Cl_2, -5°C, 0.5 h then add **20**. b) $Me_3O^+BF_4^-$/"proton sponge™"/ CH_2Cl_2, r.t. c) HF(5%)/CH_3CN, r.t.

Synthesis of the tetrahydropyran portion of the molecule (Scheme 6) began with alkylation of (*S*)-dimethyl malate **25** with LDA/MeI, according to the procedure reported by Seebach,[22] which led to a 91:9 mixture of R/S epimers, **26**. This mixture was then protected as the THP ether **27**, reduced to the diol **28**, and deprotected to the triol **29**. Attempted selective protection of the 1,2-diol function of **29** with *p*-toluenesulphonic

acid in acetone was complicated by the formation of 12% of the 1,3-dioxane. Both of these compounds were present as a mixture of methyl-epimers, and neither the regioisomers nor the epimers could be chromatographically separated. Formation of 10-15% dioxane in analogous systems has been reported in the literature[23] although, curiously, few researchers refer to this phenomenon. The formation of dioxane was completely suppressed by the use of 3-pentanone rather than acetone,[24] and furthermore, the 91:9 mixture of epimeric dioxolanes could be chromatographically separated to yield compound **30** as a single diastereoisomer in 56% overall yield from **26**, with no purification of intermediates. Conversion to the iodide **32** proceeded uneventfully using standard methodology.



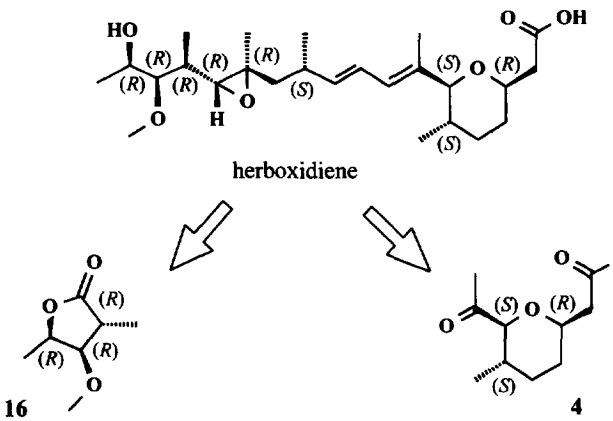
Scheme 6.

Reagents and Conditions. a) LDA/MeI/THF, -78°C. b) p-TsOH/dihydropyran/CH_2Cl_2, r.t. c) $LiAlH_4/Et_2O$, 0°C. d) IR-120/MeOH, r.t. e) p-TsOH/3-pentanone/THF, reflux, then separation by flash chromatography. f) p-TsCl/Pyr, 0°C to r.t. g) NaI/acetone, reflux. h) LDA/THF/HMPA/**33**, 0°C then add **32**. i) p-TsOH/CH_2Cl_2, reflux. j) $Et_3SiH/TiCl_4/CH_2Cl_2$, -78° to -25°. k) DMSO/$(COCl)_2/CH_2Cl_2$ -78°C then add **36**, Et_3N, -78°C to r.t. l) MeMgBr/Et_2O, -78°C to -40°C. m) CrO_3/H_2SO_4/acetone, r.t.

The next step in the synthesis was the nucleophilic displacement of the iodide moiety with the dianion of methyl acetoacetate **33**, analogous to the method of Kotsuki.[15] The dianion was generated by treatment of **33** with 2.2eq. of LDA in THF followed by slow addition of **32**. The yield of the required β-ketoester **34** obtained from this procedure was poor as the major reaction pathway was elimination of HI from **32**. The latter reaction

was completely suppressed when the reaction was carried out in the presence of HMPA, and **34** could be obtained in 74% isolated yield. Treatment of this acetal with p-TsOH in refluxing methylene chloride resulted in clean formation of bicyclic acetal **35**. The key reduction was carried out with $Et_3SiH/TiCl_4$ in methylene chloride commencing at -78°C and allowing to warm to -25°C over 90 minutes. Only when the mixture approached -25°C did the reaction proceed at an appreciable rate. Work up and purification by flash chromatography provided the desired alcohol **36** in 71% yield as a single diastereoisomer as evidenced by GC and NMR analysis. Completion of the synthesis was achieved by Swern oxidation, treatment of the resultant aldehyde **37** with methyl magnesium bromide, and subsequent oxidation of the resultant diastereoisomeric diols with Jones reagent.

The identical spectral data and, more significantly, the optical rotation values of the synthetic materials when compared with those of the fragments obtained from degradation of herboxidiene, unambiguously showed the absolute configuration of the natural product to be that depicted in Figure 2.



$[\alpha]_D$ = + 29.2° (from synthesis.)
$[\alpha]_D$ = + 29.9° (from degradation)

$[\alpha]_D$ = - 94.1° (from synthesis.)
$[\alpha]_D$ = - 92.5° (from degradation)

Figure 2. Absolute configuration of herboxidiene

In conclusion, the absolute configuration of herboxidiene has been determined by a combination of degradation of the natural product, and independent asymmetric synthesis of the respective fragments. The advantage of the cleavage procedure is that seven of the stereogenic centres of the natural product are conserved, and the E-geometry of the C8-C9 double bond of the natural product is retained. In comparison to the ozonolytic cleavage, fragments obtained by this method (**11**, **16** and **18**) are thus much more useful intermediates for preparation of analogues of the natural product. These studies will be reported in a forthcoming paper.

EXPERIMENTAL

General. All reactions were carried out under Ar with magnetic stirring, unless otherwise specified. Solvents were dried by distillation from drying agents as follows: Et_2O (Na), THF (Na), toluene (K), CH_2Cl_2 and HMPA (CaH_2). Work-up denotes extraction with an organic solvent, drying (Na_2SO_4 or $MgSO_4$) and evaporation. Flash column chromatography (FC): SiO_2 (Merck 60). M.p.: *Kofler* hot stage; uncorrected. $[\alpha]_D$: *Perkin-Elmer-241* polarimeter, in $CHCl_3$ at 20 °C, unless otherwise specified. IR: *Perkin-Elmer 1600 FTIR*, solids as a solution in $CHCl_3$, oils as a natural film on NaCl plates. ^1H NMR at 300 or 400 MHz in $CDCl_3$,

standard $CHCl_3$ (δ = 7.26 ppm), *J* in Hz. ^{13}C NMR at 75.4 or 100.62 MHz in $CDCl_3$, standard $CDCl_3$ (δ = 77.0 ppm), unless otherwise specified. Multiplicity's for ^{13}C NMR where given were obtained using DEPT Spectroscopy. Assignments in ^{13}C NMR and ^1H NMR where given were determined using 2D-$^1H/^{13}C$ HETCOR and COSY experiments respectively. MS: *Varian CH-4* or *Finingen 4023*, *m/z* (el.-%). GC: *Hewlett-Packard 5890 A*, integrator *HP 3390 A*, column HP-1 (cross linked methyl siloxane) 10 m x 0.53 mm x 2.65 µm film thickness, carrier gas He (30 ml^3/min), 70 °C/1 min then 30 °C per min to 250 °C unless otherwise specified.

Ozonolysis of herboxidiene

Herboxidiene (1.0 g, 2.3 mmol) was dissolved in CH_2Cl_2:MeOH (3:1, 40 ml) and cooled to -78 °C. A stream of ozone was bubbled through the solution until the light blue colour persisted. Dimethyl sulphide (1.132 g, 18.25 mmol) was added and the mixture allowed to warm to r.t.. The reaction mixture was diluted with CH_2Cl_2 and then washed with sat. aq. $NaHCO_3$. The organic phase was washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FC (hexane:EtOAc, 6:1) gave 523 mg (94%) of the unstable 3-[3(*R*)-hydroxy-2(*R*)-methoxy-1(*R*)-methyl-butyl)-2(*R*)-methyl-oxiranyl]-2(*S*)-methyl-propion-aldehyde (**3**) as a colourless oil. GC (92.3%), ret. time 4.81 min.

^1H NMR (200 MHz): 0.97 (*d*, *J* = 6, 3 H); 1.17 (*d*, *J* = 7.6, 3 H); 1.19 (*d*, *J* = 7.6, 3 H); 1.30 (*s*, 3 H); 1.49-1.68 (*m*, 1 H); 1.65 (*dd*, *J* = 14.4, 5.7, 1 H); 1.95 (*dd*, *J* = 14.4, 8, 1 H); 2.40-2.62 (*m*, 1 H); 2.63 (*d*, *J* = 10.2, 1 H); 2.97 (*t*, *J* = 6, 1 H); 3.56 (*s*, 3 H); 3.86 (*qi*, *J* = 6, 1 H); 9.58 (*d*, *J* = 3, 1 H).

MS: 226 (8, $[C_{13}H_{24}O_4\text{-}H_2O]^+$); 156 (9); 129 (4); 109 (20); 100 (17); 97 (100); 95 (25); 71 (15); 69 (40); 67(13); 55 (16); 53 (11); 43 (68); 41 (50).

The compound decomposed before further characterisation was possible.

[6(*S*)-Acetyl-5(*S*)-methyl-tetrahydropyran-2(*R*)-yl]-acetic acid (2)

The aqueous phase from above was diluted with EtOAc and acidified with 10% aq. HCl. The organic phase was removed and washed with water until neutral. Drying over Na_2SO_4 and concentration *in vacuo* gave 356 mg (78%) of the acid **2** as a viscous oil. GC (97.3%), ret. time 4.95 min. $[\alpha]_D$ = -68.5, $[\alpha]_{578}$ = -72.1, $[\alpha]_{546}$ = -84.8, $[\alpha]_{436}$ = -181.3, $[\alpha]_{365}$ = -431.5 (c = 1.28).

^1H NMR: 0.83 (*d*, *J* = 6.5, 3 H); 1.21-1.38 (*m*, 1 H); 1.39-1.47 (*m*, 1 H); 1.49-1.61 (*m*, 1 H); 1.73 (*ddd*, *J* = 12.5, 5.5, 2, 1 H); 1.90 (*ddd*, *J* = 13, 7, 3.5, 1 H); 2.16 (*s*, 3 H); 2.51 (*dd*, *J* = 14.5, 7.1, 1 H); 2.62 (*dd*, *J* = 14.5, 7.1, 1 H); 3.44 (*d*, *J* = 10.5, 1 H); 3.75-3.86 (*m*, 1 H).

^{13}C NMR: 208.46 (*s*); 176.27 (*s*); 88.74 (*d*); 73.30 (*d*); 40.79 (*t*); 32.26 (*t*); 31.82 (*q*); 31.50 (*t*); 25.47 (*d*); 16.52 (*q*).

MS: 172 (0.2, $[C_{10}H_{16}O_4\text{-}CO]$+.); 171 (1.4); 157 (13); 140 (2); 139 (19); 121(3); 111 (7); 97 (29); 95 (7); 93 (7); 42 (100).

[6(*S*)-Acetyl-5(*S*)-methyl-tetrahydropyran-2(*R*)-yl]-acetic acid methyl ester (4)

The crude sample from above (300 mg, 1.50 mmol) was dissolved in 20 ml of sat. anhydrous methanol/HCl and stirred at reflux for 4 h. The solution was then diluted with EtOAc and neutralised with sat. aq. $NaHCO_3$. Drying over Na_2SO_4 and concentration *in vacuo* gave the crude product which was further purified by FC (hexane:EtOAc, 5:1) yielding the title compound (308 mg, 96%) as a colourless oil. GC (99.7%), ret. time 4.95 min. $[\alpha]_D$ = -92.5, $[\alpha]_{578}$ = -95.0, $[\alpha]_{546}$ = -112.5, $[\alpha]_{436}$ = -242.5, $[\alpha]_{365}$ = -590.0 (c = 0.4).

IR: 2950, 2930, 2850, 1741, 1719, 1440, 1350, 1280, 1200, 1160, 1080, 1020, 890.

^1H NMR: 0.83 (*d*, *J* = 6.5, 3 H); 1.22-1.34 (*m*, 1 H); 1.35-1.47 (*m*, 1 H); 1.49-1.61 (*m*, 1 H); 1.71 (*ddd*, *J* = 12.5, 5.5, 2, 1 H); 1.89 (*ddd*, *J* = 13, 7, 3.5, 1 H); 2.15 (*s*, 3 H); 2.46 (*dd*, *J* = 15, 5, 1 H); 2.59 (*dd*, *J* = 15, 7.5, 1 H); 3.42 (*d*, *J* = 10.5, 1 H); 3.69 (*s*, 3 H); 3.76-3.84 (*m*, 1 H).

^{13}C NMR: 207.55 (*s*); 171.40 (*s*); 89.02 (*d*); 73.81 (*d*); 51.55 (*q*); 41.17 (*t*); 32.26 (*t*); 31.80 (*q*); 31.12 (*t*); 25.69 (*d*); 16.86 (*q*).

MS: 215 (0.2, $[C_{11}H_{18}O_4+H]^+$); 172 (31); 171 (13); 140 (27); 139 (35); 111 (32); 97 (81); 95 (25); 93 (37); 85 (18); 69 (52); 59 (59); 55 (100).
Anal. calc. for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.56; H, 8.56.

1(*R*)-[2(*R*),4(*S*)-Dimethyl-tetrahydrofuran-2-yl]-3(*R*)-methoxy-2(*R*)-methyl-pentane-1-4(*R*)-diol (5)

A solution of **3** (60 mg, 0.247 mmol) in 4 ml of MeOH:THF (1:1) was treated at r.t. with sodium borohydride (11.7 mg, 0.306 mmol). After reaction completion (*ca.* 10 min), EtOAc was added and the mixture washed successively with 10% aq. HCl, water, and sat. aq. $NaHCO_3$. Drying over Na_2SO_4, concentration *in vacuo*, and purification by FC (hexane:EtOAc 3:1) gave **5** (57 mg, 94%) as a colourless oil.
^{1}H NMR: 0.81 (*d*, *J* = 7.5, 3 H); 1.00 (*d*, *J* = 6.6, 3 H); 1.18 (*d*, *J* = 6.6, 3 H); 1.20 (*s*, 3 H); 1.40-1.61 (*m*, 1 H); 1.65-1.83 (*m*, 2 H); 2.20-2.41 (*m*, 1 H); 3.20-3.41 (*m*, 2 H); 3.48 (*d*, *J* = 9, 1 H); 3.52 (*s*, 3 H); 3.81 (*qi*, *J* = 6.6, 1 H); 3.95 (*t*, *J* = 7.5, 1 H).

The structure of the compound was confirmed by conversion to the diacetate **6** as follows: A solution of **5** (25 mg, 0.102 mmol) in pyridine (4ml) was treated with Ac_2O (31 mg, 0.304 mmol) at r.t. The mixture was stirred for 18 h, diluted with EtOAc, and washed successively with 10% aq. HCl, water, and sat. aq. $NaHCO_3$. Drying over Na_2SO_4 and concentration *in vacuo*, followed by FC (hexane:EtOAc 9:1) gave 32 mg (96%) of the diacetate **6** as a colourless oil.
^{1}H NMR: 1.04 (*d*, *J* = 6.6, 3 H); 1.06 (*d*, *J* = 6.6, 3 H); 1.20 (*s*, 3 H); 1.21 (*d*, *J* = 6.6, 3 H); 1.40-1.60 (*m*, 1 H); 1.80 (*dd*, *J* = 18, 6, 1 H); 1.87-2.04 (*m*, 1 H); 2.09 (*s*, 3 H); 2.12 (*s*, 3 H); 2.25-2.48 (*m*, 1 H); 3.25 (*dd*, *J* = 10.1, 5.5, 1 H); 3.35 (*dd*, *J* = 10.1, 2.5, 1 H); 3.46 (*s*, 3 H); 3.90 (*t*, *J* = 7.6, 1 H); 4.90 (*d*, *J* = 7.6, 1 H); 5.05 (*qi*, *J* = 6.6, 1 H).
Anal. calc. for $C_{17}H_{30}O_6$: C, 61.80; H, 9.15. Found: C, 61.91; H, 9.19.

Herboxidiene Methyl Ester (8)

Herboxidiene (1.0 g, 2.3 mmol) was dissolved in DMF (25ml) and treated with anhydrous K_2CO_3 (346 mg, 2.51 mmol) and dimethyl sulphate (316 mg, 2.51 mmol). The reaction mixture was vigorously stirred and warmed to 90 °C. Analysis by TLC showed the reaction to be complete in *ca.* 20 min. Normal aqueous work-up, and purification by FC (hexane:EtOAc 5:1) gave the title compound (950 mg, 92%) as a colourless oil. The spectral data of the methyl ester obtained were in agreement with those reported in reference 1.

{6(*S*)-[7(*R*)-Hydroxy-7-(4(*R*)-methoxy-3(*R*),5(*R*)-dimethyl-tetrahydrofuran-2(*S*)-yl)-1,5(*S*)-dimethyl-octa-1,3(E,E)-dienyl]-5(*S*)-methyltetrahydro-pyran-2(*R*)-yl}-acetic acid methyl ester (7)

A solution of **8** (1.0 g, 2.3 mmol) in MeOH (10ml) was treated with a solution of anhydrous HCl/MeOH (*ca.* 11 M, 20 ml) at r.t.. After the addition, the reaction mixture was immediately poured onto a mixture of crushed ice, sat. aq. $NaHCO_3$, and EtOAc. Aqueous work-up and purification by FC (hexane:EtOAc 12:1) gave the title compound **7** (601 mg, 60%) as a colourless oil. The spectral data for this compound were identical to those given in reference 1.

Glycol cleavage of {6(*S*)-[7(*R*)-hydroxy-7-(4(*R*)-methoxy-3(*R*),5(*R*)-dimethyl-tetrahydrofuran-2(*S*)-yl)-1,5(*S*)-dimethyl-octa-1,3(E,E)-dienyl]-5(*S*)-methyltetrahydropyran-2(*R*)-yl}-acetic acid methyl ester (7)

A solution of **7** (5.92 g, 13.1 mmol) in acetone:water (3:1, 40ml) was treated at r.t. with N-methyl morpholine oxide (2.29 g, 19.62 mmol). Osmium tetroxide (200 mg in 0.2 ml t-BuOH) was added not allowing the temperature to rise above 25 °C. The reaction was stirred at r.t. and shown by TLC analysis (hexane:EtOAc 1:1) to be complete after *ca.* 3 h. The reaction mixture was diluted with EtOAc and washed with 10% aq. $NaHSO_3$, then water, dried over Na_2SO_4 and then concentrated *in vacuo*. The crude mixture of diastereoisomeric diols **9** (6.01 g, 94%) were taken up in 4:1 THF:H_2O (50 ml) and treated at r.t. with sodium metaperiodate (2.91 g, 13.6 mmol). A floculent white precipitate formed and TLC analysis after 15 min showed reaction completion. Normal aq. work up gave a crude product which was further purified by FC (hexane:EtOAc 8:1). The first eluted product was [5(*S*)-methyl-6(*S*)-(E-1-methyl-3-oxopropenyl)-

tetrahydropyran-2(*R*)-yl]-acetic acid methyl ester (**11**) as a colourless oil (2.18 g, 74%). $[\alpha]_D$ = +56.7; $[\alpha]_{578}$ = +60.5; $[\alpha]_{546}$ = +73.2; $[\alpha]_{436}$ = +197.9; $[\alpha]_{365}$ = +610.6 (c = 0.4).
IR: 2950, 2930, 2850, 1740, 1677, 1440, 1200, 1100, 1070, 1020.
^{1}H NMR: 0.74 (*d*, *J* = 6.5, 3 H); 1.23-1.45 (*m*, 2 H); 1.49-1.61 (*m*, 1 H); 1.69-1.76 (*m*, 1 H); 1.86-1.93 (*m*, 1 H); 2.14 (*s*, 3 H); 2.43 (*dd*, *J* = 15.5, 6, 1 H); 2.57 (*dd*, *J* = 15.5, 7, 1 H); 3.49 (*d*, *J* = 10, 1 H); 3.67 (*s*, 3 H); 3.78-3.86 (*m*, 1 H); 5.92 (*d*, *J* = 7.5, 1 H); 10.06 (*d*, *J* = 7.5, 1 H).
^{13}C NMR: 191.42 (*d*); 171.51 (*s*); 159.86 (*s*); 128.61 (*d*); 89.09 (*d*); 73.90 (*d*); 51.61 (*q*); 41.11 (*t*); 32.52 (*q*); 32.18 (*t*); 31.33 (*t*); 17.42 (*d*); 13.08 (*q*).
MS: 239 (1, $[C_{13}H_{20}O_4\text{-}H]^+$); 238 (7); 211 (5); 183 (9); 149 (13); 101 (35); 91 (24); 74 (35); 59 (100).
Anal. calc. for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.13; H, 8.43.

Continued elution gave the hemiacetal 4'(*R*)-methoxy-2(*R*),4(*S*),3'(*R*),5'(*R*)-tetramethyl-octahydro-[2,2']-bifuranyl-5-ol (**10**) as a colourless oil, virtually as a single diastereoisomer (2.32 g, 77%). $[\alpha]_D$ = -44.3; $[\alpha]_{578}$ = -46.5; $[\alpha]_{546}$ = -52.9; $[\alpha]_{436}$ = -92.4; $[\alpha]_{365}$ = -146.3 (c = 0.51).
^{1}H NMR: 0.86 (*d*, *J* = 7.2, 3 H, CH_3-4); 1.06 (*d*, *J* = 7.5, 3 H, CH_3-6'). 1.12-1.20 (*m*, 1 H, H-3a); 1.22 (*d*, *J* = 6.6, 3 H, CH_3-5' 1.30 (*s*, 3 H, CH_3-2); 2.20-2.32 (*m*, 2 H, H-4, H-3'); 2.45 (*dd*, *J* = 12.5, 8.3, 1 H, H-3b); 3.34 (*s*, 3 H, OCH_3); 3.37 (*d*, *J* = 4, 1 H, H-4'); 4.08 (*d*, *J* = 4.3, 1 H, H-2'). 4.36 (*dq*, *J* = 6.6, 4, 1 H, H-5'); 4.92 (*dd*, *J* = 10.7, 9, 1 H, H-5).
^{13}C NMR: 104.02 (C-5); 88.95 (C-4'); 85.90 (C-2); 84.07 (C-2'); 76.44 (C-5'); 57.46 (OCH_3); 44.05 (C-4); 39.14 (C-3'); 36.46 (CH_3-3); 26.00 (CH_3-5'); 19.58 (CH_3-2); 14.58 (CH_3-3'); 13.28 (CH_3-4).
MS: 226 (6, $[C_{13}H_{24}O_4\text{-}H_2O]^+$); 156 (9); 129 (4); 123 (3); 109 (20); 100 (18); 97 (100); 96 (93); 71 (16); 69 (40); 67 (12); 55 (18); 43 (75).
Anal. calc. for $C_{13}H_{24}O_4$: C, 63.91; H, 9.90. Found: C, 63.96; H, 9.94.

[6(*S*)-(E-3-Hydroxy-1-methyl-3-propenyl)-5(*S*)-methyl-tetrahydropyran-2(*R*)-yl]-acetic acid methyl ester (12)

A solution of **11** (3.60 g, 15.06 mmol) in 3:1 THF:MeOH (25 ml) was treated at r.t. with sodium borohydride (715 mg, 18.80 mmol). After gas evolution had ceased TLC analysis (hexane:EtOAc 2:1) showed reaction completion. The reaction mixture was diluted with EtOAc, and then washed successively with 10% aq. HCl, water, and then sat. aq. $NaHCO_3$. Drying over Na_2SO_4, concentration *in vacuo* and purification by FC (hexane:EtOAc 5:1) gave **12** (3.52g, 97%) as a colourless oil. $[\alpha]_D$ = +16.8; $[\alpha]_{578}$ = +17.7; $[\alpha]_{546}$ = +20.5; $[\alpha]_{436}$ = +38.8; $[\alpha]_{365}$ = +72.6 (*c* = 1.35).
^{1}H NMR($CDCl_3$:CD_3OD, 9:1): 0.58 (*d*, *J* = 6.6, 3 H); 1.05-1.30 (*m*, 2 H); 1.30-1.46 (*m*, 1 H); 1.48 (*s*, 3 H); 1.54 (*ddd*, *J* = 13, 4, 2.5, 1 H); 1.71 (*ddd*, *J* = 13, 6.5, 4, 1 H); 2.28 (*dd*, *J* = 15.6, 6.3, 1 H); 2.42 (*dd*, *J* = 15.6, 6.9, 1 H); 3.20 (*d*, *J* = 9.9, 1 H); 3.53 (*s*, 3 H); 3.58-3.68 (*m*, 1 H); 3.97 (*dd*, *J* = 13.2, 6.6, 1 H); 4.05 (*dd*, *J* = 13.2, 6.6, 1 H); 5.41 (*t*, *J* = 6.6, 1 H).
^{13}C NMR: 171.74; 136.40; 128.00; 89.77; 73.57; 58.36; 51.28; 40.88; 31.84; 31.56; 31.25; 17.29; 11.46.
MS: 242 (2, $[C_{13}H_{22}O_4]^+$); 224 (11); 211 (25); 195 (6); 179 (10); 151 (15); 137 (18); 111 (9); 101 (23); 83 (27); 71 (40); 59 (72); 41 (100). Anal. calc. for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.53; H, 9.32.

4(*R*)-(4(*R*)-Methoxy-3(*R*),5(*R*)-dimethyl-tetrahydrofuran-2(*S*)-yl)-2(*S*)-methyl-pentane-1,4-diol (13)

A solution of **10** (3.40 g, 13.91 mmol) in 3:1 THF:MeOH (25 ml) was treated at r.t. with sodium borohydride (635 mg, 16.70 mmol) at 0 °C. The reaction was allowed to warm to r.t., diluted with EtOAc, and then washed successively with 10% aq. HCl, water, and then sat. aq. $NaHCO_3$. Drying over Na_2SO_4, and concentration *in vacuo* gave the crude product which was further purified by FC (hexane:EtOAc 5:1). This yielded **13** (3.32g, 97%) as a colourless oil. $[\alpha]_D$ = -63.5; $[\alpha]_{578}$ = -66.8; $[\alpha]_{546}$ = -75.8; $[\alpha]_{436}$ = -129.1; $[\alpha]_{365}$ = -202.8 (c = 0.43). ^{1}H NMR: 1.01 (*d*, *J* = 6.6, 3 H); 1.03 (*d*, *J* = 6.6, 3 H); 1.19 (*d*, *J* = 6.6, 3 H); 1.26 (*s*, 3 H); 1.48 (*dd*, *J* = 14.4, 5.4, 1 H); 1.54 (*dd*, *J* = 10.5, 7.2, 1 H); 1.94-2.05 (*m*, 1 H); 2.35 (*dq*, *J* = 6.6, 3, 1 H); 3.33 (*d*, *J* = 3, 1 H); 3.36 (*s*, 3 H); 3.40 (*dd*, *J* = 13.2, 6.6, 1 H); 3.51 (*dd*, *J* = 10.5, 5.4, 1 H);3.79 (*d*, *J* = 2.5, 1 H); 4.291 (*dq*, *J* = 6.6, 2.5, 1 H).

^{13}C NMR: 89.65; 83.92; 75.21; 73.26; 68.80; 57.43; 41.83; 39.40; 31.62; 26.51; 18.62; 14.91; 14.11.
MS: 228 (2, $[C_{13}H_{26}O_4\text{-}H_2O]^{+\cdot}$); 213 (3); 173 (5); 129 (20); 137 (18); 117 (89); 99 (100); 85 (24); 69 (80).
Anal. calc. for $C_{13}H_{26}O_4$: C, 63.39; H, 10.64. Found: C, 63.40; H, 10.71.

5-(tert.-Butyl-dimethyl-silanoxy)-2(*R*)-(4'(*R*)-methoxy-3'(*R*),5'(*R*)-dimethyl-tetrahydrofuran-2'(*S*)-yl)-4(*S*)-methyl-pentan-2-ol (14)

A solution of **13** (2.80 g, 11.37 mmol), imidazole (1.16 g, 17.05 mmol) and DMAP (150 mg, 1.23 mmol) in DMF (25 ml) was cooled to 0 °C and then treated with tert-butyldimethyl chlorosilane (TBDMSCl, 1.88g, 12.52 mmol). The reaction was allowed to warm to r.t. and shown to be complete (TLC analysis) after *ca.* 30 min. The mixture was diluted with CH_2Cl_2 and then washed successively with 10% aq. HCl, water, and then sat. aq. $NaHCO_3$. Drying over Na_2SO_4, and concentration *in vacuo* gave **14** (3.65 g, 89%) as a colourless oil which was used in the next step without further purification. GC (98%), ret. time. 5.95 min. An analytical sample had the following spectral data: $[\alpha]_D$ = -42.5; $[\alpha]_{578}$ = -42.6; $[\alpha]_{546}$ = -48.6; $[\alpha]_{436}$ = -83.1; $[\alpha]_{365}$ = -130.2 (c = 0.65).
^{1}H NMR: 0.04 (*s*, 6 H); 0.88 (*s*, 9 H); 0.97 (*d*, *J* = 6.6, 3 H); 1.05 (*d*, *J* = 7.2, 3 H); 1.18 (*d*, *J* = 6.6, 3 H); 1.24 (*s*, 3 H); 1.39 (*dd*, *J* = 14.4, 7.8, 1 H); 1.54 (*dd*, *J* = 14.4, 4.3, 1 H); 1.83-1.97 (*m*, 1 H); 2.36 (*br qi*, *J* = 6.6, 1 H); 2.51 (*br s*, OH); 3.30 (*dd*, *J* = 9.6, 7.8, 1 H); 3.33 (*s*, 3 H); 3.35 (*d*, *J* = 2.1, 1 H); 3.43 (*dd*, *J* = 9.6, 5.4, 1 H); 3.78 (*d*, *J* = 4.8, 1 H); 4.29 (*dq*, *J* = 6.6, 2.1, 1 H).
^{13}C NMR: 89.90; 83.84; 75.33; 72.51; 69.47; 57.52; 41.24; 39.36; 31.57; 26.56; 25.88 (3C); 18.51; 18.25; 14.98; -5.45; -5.50.
MS: 345 (0.5, $[C_{19}H_{40}O_4Si\text{-}CH_3]^{+\cdot}$); 231 (5); 177 (7); 145 (2); 139 (1); 137 (2); 123 (15); 109 (3); 99 (69); 89 (5); 75 (36); 73 (14); 69 (24); 67 (4); 55 (13); 45 (12); 43 (100).
Anal. calc. for $C_{19}H_{40}O_4Si$: C, 63.29; H, 11.19. Found: C, 63.40; H, 11.36.

Oxidative Cleavage of 5-(tert.-butyl-dimethyl-silanoxy)-2(*R*)-(4'(*R*)-methoxy-3'(*R*),5'(*R*)-dimethyl-tetrahydrofuran-2'(*S*)-yl)-4(*S*)-methyl-pentan-2-ol (14)

Powdered 4Å molecular sieves (8 g) were flame dried under nitrogen in a glass reaction vessel. After cooling, CH_2Cl_2 (150 ml) was added together with pyridinium chlorochromate (8.62 g, 40.0 mmol). A solution of **14** (3.60g, 10 mmol) in CH_2Cl_2 (10 ml) was added and the reaction brought to reflux. Monitoring by TLC (hexane:EtOAc 5:1) and GC showed reaction completion after *ca.* 3 h. The mixture was diluted with Et_2O and filtered over hyflo. The filter cake was thoroughly washed with Et_2O and the filtrate then carefully concentrated *in vacuo* to give a dark brown tar. GC analysis of this residue showed peaks at 2.43 min, 3.39 min and 5.08 min in a ratio of 5:13:1, respectively. This residue was purified by FC (pentane:Et_2O 4:1) to give as the first eluted product 5(tert-butyl-dimethyl-silanyloxy)-4(*S*)-methyl-pentan-2-one (**17**) (1.73g, 75%). GC (99.7%), ret. time 3.39 min. $[\alpha]_D$ = +19.2; $[\alpha]_{578}$ = +19.2; $[\alpha]_{546}$ = +24.5; $[\alpha]_{436}$ = +50.0; $[\alpha]_{365}$ = +245.2 (c = 0.52).
^{1}H NMR: 0.00 (*s*, 6 H); 0.86 (*d*, *J* = 6, 3 H); 0.86 (*s*, 9 H); 2.06-2.20 (*m*, 2 H); 2.11 (*s*, 3 H); 2.52-2.61 (*m*, 1 H); 3.33 (*dd*, *J* = 10, 6.6, 1 H); 3.46 (*dd*, *J* = 10, 5.4, 1 H).
^{13}C NMR: 207.90; 66.80; 46.84; 31.48; 29.66; 25.22 (3C); 17.62; 16.05; -6.10 (2C).
MS: 215 (1, $[C_{12}H_{26}O_2\ Si\text{-}H_2O]^{+\cdot}$); 173 (100); 155 (47); 129 (28); 137 (18); 115 (29); 103 (8); 99 (17); 81 (22); 75 (98); 61 (16); 59 (26); 43 (74).
Anal. calc. for $C_{12}H_{26}O_2$ Si: C, 62.55; H, 11.37. Found: C, 62.60; H, 11.45.

The second eluted product was 4(*R*)-methoxy-3(*R*),5(*R*)-dimethyl-dihydro-furan-2-one (**16**) (1.15g, 80%). GC (99.9%), ret. time 2.43 min. $[\alpha]_D$ = +29.9; $[\alpha]_{578}$ = +31.9; $[\alpha]_{546}$ = +36.9; $[\alpha]_{436}$ = +58.3; $[\alpha]_{365}$ = +78.8 (c = 0.20).
^{1}H NMR: 1.30 (*d*, *J* = 7,2, 3H, CH_3-3); , 1.34 (*d*, *J* = 6,3, 3 H, CH_3-5); 2.66 (*dq*, *J* = 7.2, 6.3, 1 H, H-3); 3.36 (*s*, 3 H, OCH_3); 3.66 (*t*, *J* = 6.3, 1 H, H-4); 4.71 (*qi*, *J* = 6.3, 1 H, H-5).
^{13}C NMR: 176.82 (*s*); 83.66(*d*); 76.47 (*d*); 57.48 (*q*); 39.72 (*d*); 14.02(*q*); 13.48 (*q*).
MS: 144 (0.2, $[C_7H_{12}O_3]^{+\cdot}$); 129 (0.25); 116 (1.4); 99 (0.36); 85 (2); 72 (100); 57 (18); 44 (3).
Anal. calc. for $C_7H_{12}O_3$: C, 58.32; H, 8.39. Found: C, 58.38; H, 8.47.

The final product to be eluted was 4'(*R*)-methoxy-2(*R*),4(*S*),3'(*R*),5'(*R*)-tetramethyl-tetrahydro-[2,2'(*S*)]-bifuranyl-5-one (**19**) (170 mg, 7%). M.p = 47-48 °C. GC (100%), ret. time 5.08 min. $[\alpha]_D$ = -50.6; $[\alpha]_{578}$ = -52.6; $[\alpha]_{546}$ = -59.8; $[\alpha]_{436}$ = -101.4; $[\alpha]_{365}$ = -157.9 (c = 0.85).
^{1}H NMR: 0.99 (*d*, *J* = 7.2, 3H, CH_3-3'); 1.15 (*d*, *J* = 6.6, 3 H, CH_3-5'); 1.24 (*d*, *J* = 7.5, 3H, CH_3-4); 1.42 (*s*, 3 H, CH_3-2); 1.52 (*dd*, *J* = 12.9, 9.9, 1 H, H-3a); 2.32 (*qi*, *J* = 7.2, 1 H, H-3'). 2.62 (*dd*, *J* = 12.9, 9.9, 3 H, H-3b); , 2.84-3.01 (*m*, 1 H, H-4); 3.34 (*s*, 3H, OCH_3); 3.36 (*d*, *J* = 4.2, 1 H, H-4'); 4.09 (*d*, *J* = 5.1, 1 H, H-2'); 4.34 (*dq*, *J* = 6.6, 4.2, 1 H, H-5').
^{13}C NMR: 179.53; 88.73; 85.43; 82.58; 76.37; 57.76; 39.96; 39.11; 36.10; 24.92; 16.63; 14.82; 13.67.
MS: 242 (2, $[C_{13}H_{22}O_4]^{+\cdot}$); 227 (0.05); 156 (1); 129 (85); 113 (20); 101(10); 97 (11); 85 (15); 69 (85); 55 (11); 43 (100).
Anal. calc. for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.48; H, 9.21.

5-(tert.-Butyl-diphenyl-silanoxy)-2(*R*)-(4'(*R*)-methoxy-3'(*R*),5'(*R*)-dimethyl-tetrahydrofuran-2'(*S*)-yl)-4(*S*)-methyl-pentan-2-ol (15)

A solution of **13** (1.50 g, 6.10 mmol), imidazole (622 mg, 9.15 mmol) and DMAP (100 mg, 0.82 mmol) in DMF (20 ml) was cooled to 0 °C and then treated with tert-butyldiphenyl chlorosilane (TBDPSCl, 2.01 g, 7.32 mmol). The solution was allowed to warm to r.t. and shown to be complete (TLC analysis) after *ca.* 60 min The mixture was diluted with CH_2Cl_2 and then washed successively with 10% aq. HCl, water, and then sat. aq. $NaHCO_3$. Drying over Na_2SO_4, and concentration *in vacuo* gave **15** (2.29 g, 88%) as a colourless oil which was used in the next step without further purification. GC (98%), ret. time. 7.41 min. An analytical sample had the following spectral data. $[\alpha]_D$ = -28.2; $[\alpha]_{578}$ = -29.5; $[\alpha]_{546}$ = -33.8; $[\alpha]_{436}$ = -57.1; $[\alpha]_{365}$ = -89.7 (c = 0.85).
^{1}H NMR: 1.01 (*d*, *J* = 6.6, 3 H, CH_3-4); 1.04 (*d*, *J* = 6.6, 3 H, CH_3-3'); 1.06 (*s*, 9 H, t-Bu); 1.20 (*d*, *J* = 6.6, 3 H, CH_3-5'); 1.23 (*s*, 3 H, CH_3-2); 1.39 (*dd*, *J* = 14.1, 8.4, 1 H, H-3a); 1.60 (*dd*, *J* = 14.1, 3.6, 1 H, H-3b); 1.91-2.10 (*m*, 1 H, H-4); 2.28 (*br s*, 1 H, OH); 2.33 (*br q*, *J* = 6.6, 1 H, H-3'); 3.32 (*s*, 3 H, OCH_3); 3.34 (*d*, *J* = 2.1, 1 H, H-4'); 3.40 (*dd*, *J* = 9.9, 7.2, 1 H, H-5a); 3.48 (*dd*, *J* = 9.9, 5.7, 1 H, H-5b); 3.76 (*d*, *J* = 4.2, 1 H, H-2'); 4.29 (*dq*, *J* = 6.6, 2.1, 1 H, H-5'). 7.35-7.50 (*m*, 6 H); 7.69 (*d*, *J* = 7.4, 4 H).
^{13}C NMR: 135.64 (4C); 133.87 (2C); 128.6 (2C); 127.64 (4C); 89.81; 84.10; 75.32; 73.41; 70.06; 57.40; 40.29; 39.22; 31.49; 26.76 (3C); 26.46; 19.13; 18.46; 14.91; 14.03.
MS: 469 (0.2, $[C_{29}H_{44}O_4Si\text{-}CH_3]^{+\cdot}$); 355 (4); 297 (2); 277 (8); 221 (1); 199 (43); 179 (47); 149 (4); 139 (18); 135 (15); 99 (100); 85 912); 13 (83); 71 (12); 69 (43); 55 (23).
Anal. calc. for $C_{29}H_{44}O_4Si$: C, 71.85; H, 9.15. Found: C, 72.00; H, 9.36.

Oxidative cleavage of 5-(tert.-butyl-diphenyl-silanoxy)-2(*R*)-(4'(*R*)-methoxy-3'(*R*),5'(*R*)-dimethyl-tetrahydrofuran-2'(*S*)-yl)-4(*S*)-methyl-pentan-2-ol (15)

Carried out as described for **14**, using **15** (2.1 g, 4.33 mmol), powdered 4Å molecular sieves (5 g), CH_2Cl_2 (75 ml) and pyridinium chlorochromate (4.67 g, 21.69 mmol). Monitoring by TLC (hexane:EtOAc 5:1) and GC showed reaction completion after *ca.* 1 h. Work-up as described for **14** gave a residue which showed only two peaks in GC at 2.43 min and 6.71 min, with no lactone **19** being detected. The residue was purified by FC (pentane:Et_2O 4:1) to give as the first eluted product 5(tert-butyl-diphenyl-silanyloxy)-4(*S*)-methyl-pentan-2-one (**18**) (1.29g, 84%) as a colourless oil. GC (99.8%), ret. time 6.71 min. $[\alpha]_D$ = -1.9; $[\alpha]_{578}$ = -1.9; $[\alpha]_{546}$ = -1.85; $[\alpha]_{436}$ = +0.30; $[\alpha]_{365}$ = +13.5 (*c* = 7.86).
^{1}H NMR: 0.90 (*d*, *J* = 6.3, 3 H); 1.05 (*s*, 9 H); 2.12 (*s*, 3 H); 2.18-2.30 (*m*, 2 H); 2.60-2.71 (*m*, 1 H); 3.46 (*dd*, *J* = 9.6, 5.9, 1 H); 3.57 (*dd*, *J* = 9.6, 5.3, 1 H); 7.35-7.50 (*m*, 6 H); 7.69 (*d*, *J* = 7.4, 4 H).
^{13}C NMR: 208.64; 135.53 (4C); 133.62 (2C); 129.59 (2C); 127.62 (4C); 68.13; 47.37; 31.84; 26.70 (3C); 26.43; 19.10; 16.58.
MS: 297 (41, $[C_{22}H_{30}O_2Si\text{-}C(CH_3)_3]^{+\cdot}$); 219 (11); 199 (100); 181 (13); 175 (12); 105 (11); 77 (18); 57 (3).
Anal. calc. for $C_{22}H_{30}O_2Si$: C, 74.53; H, 8.53. Found: C, 74.72; H, 8.62.

The second product to be eluted was the lactone **16** (605 mg, 97%) as a colourless liquid (GC (100%), ret. time 2.43 min) which had identical spectral data to those given earlier.

2,3-Dihydro-N-[4(*R*)-silanyloxy-3(*R*)-hydroxy-2(*R*)-methyl-pentanoyl]-3(*R*)-methyl-1,2-benzothiazole-1,1-dioxide (23)

Trifluoroacetic acid (6.75 ml, 79.8 mmol) was added to a stirred 1.0 M solution of triethylborane in hexane (82.2 ml, 82.2 mmol). The mixture was stirred at 40 °C until gas evolution ceased (*ca.* 30 min). The mixture was cooled to -5 °C at which temperature was added the sultam **21** (8.88 g, 37.15 mmol) and the diisopropylethylamine (13.77 ml, 80.04 mmol) as a solution in CH_2Cl_2 (90ml). This mixture was stirred for 30 min at -5°C, cooled to -78 °C and the aldehyde **20** (10.48g, 55.73mmol) was added dropwise over 15 min. The reaction was stirred at -78 °C and monitored by TLC (hexane:CH_2Cl_2:Et_2O, 8:2:1). After 4 h the mixture was quenched by the addition of pH 7 aq. phosphate buffer and allowed to warm to r.t.. The mixture was diluted (CH_2Cl_2), and washed successively with 10% aq. HCl, water, and sat. aq. $NaHCO_3$. Drying over Na_2SO_4 and concentration *in vacuo*, followed by FC (hexane:CH_2Cl_2:Et_2O, 10:2:1) and crystallisation (CH_2Cl_2/hexane) gave 11.44 g (72%) of the aldol **23** as a colourless, crystalline solid. M.p. 120.4-120.9 °C (lit. [16] for *ent*-**23** 118-120 °C). $[\alpha]_D$ = -23.1 {lit. [16] for *ent*-**23**, $[\alpha]_D$ = +22.0 (c = 1.08)}; $[\alpha]_{578}$ = -24.1; $[\alpha]_{546}$ = -26.3; $[\alpha]_{436}$ = -41.6; $[\alpha]_{365}$ = -56.4 (c = 0.43).

IR: 3540, 3029, 2953, 2932, 2888, 2858, 1690, 1456, 1380, 1330, 1249, 1160, 1132, 1053, 838, 758, 668, 598.

^{1}H NMR: 0.09 (*s*, 6H); 0.9 (*s*, 9H); 1.23 (*d*, *J* = 6.3, 3 H); 1.45 (*d*, *J* = 7.3, 3 H); 1.65 (*d*, *J* = 6.3, 3 H); 2.77 (*d*, *J* = 5.5, 1 H); 3.44 (*m*, 1 H); 3.80-3.90 (*m*, 2 H); 5.46 (*q*, *J* = 6.3 Hz, 1 H); 7.41 (*d*, *J* = 7.8, 1 H); 7.55 (*t*, J = 7.5, 1 H); 7.68 (*t*, *J* = 7.5, 1 H); 7.77 (*d*, *J* = 7.8, 1 H).

^{13}C NMR: 173.79 (*s*); 137.12 (*s*); 134.08 (*s*); 133.62 (*d*); 129.58 (*s*); 124.26 (*d*); 121.64 (*d*); 74.90 (*d*); 70.40 (*d*); 55.42 (*d*); 43.19 (*d*); 25.84 (*q*,*3C*); 21.04 (*q*); 20.78 (*q*); 18.00 (*s*); 13.86(*q*); -4.16 (*q*); -4.88(*q*).

MS: 370 (18, $[C_{20}H_{33}NSO_5Si\text{-}C(CH_3)_3]^+$); 268 (5); 258 (7); 240 (5); 187 (21); 184 (15); 168 (10); 131 (65); 115 (20); 103 (31); 73 (100); 59 (23).

HR-MS: 370.1129 ($[C_{20}H_{33}NSO_5Si\text{-}C(CH_3)_3]^+$); calc. 370.1144).

2,3-Dihydro-N-[4(*R*)-silanyloxy-3(*R*)-methoxy-2(*R*)-methyl-pentanoyl]-3(*R*)-methyl-1,2-benzothiazole-1,1-dioxide (24)

Trimethyloxonium tetrafluoroborate (21.07 g, 140.5 mmol) and 1,8-bis-(dimethylamino)-naphthalene (31.75 g, 147.5 mmol) were added to a mechanically stirred solution of the aldol **23** (10.0g, 23.42 mmol) in CH_2Cl_2 (1000 ml) at r.t.. After 18 h the suspension was diluted (CH_2Cl_2) and washed successively with 10% aq. HCl, water, and sat. aq. $NaHCO_3$. FC (hexane/EtOAc 8:1) and crystallisation (hexane/CH_2Cl_2) gave the methyl ether **24** (10.28 g, 98%) as a colourless, crystalline solid. M.p. 87.6-88 °C. $[\alpha]_D$ = -25.1; $[\alpha]_{578}$ = -26.2; $[\alpha]_{546}$ = -30.3; $[\alpha]_{436}$ = -53.9; $[\alpha]_{365}$ = -76.9 (c = 0.2).

^{1}H NMR: 0.00 (*s*, 3 H); 0.02 (*s*, 3 H); 0.80 (*s*, 9 H); 1.17 (*d*, *J* = 6.3, 3 H); 1.38 (*d*, *J* = 6.9, 3 H); 1.62 (*d*, *J* = 6.3, 3 H); 3.43-3.52 (*m*, 1H); 3.47 (*s*, 3H); 3.59 (*t*, *J* = 6.3, 1 H); 4.00 (*qi*, *J* = 6.3, 1 H); 5.39 (*q*, *J* = 6.6 Hz, 1H); 7.41 (*d*, *J* = 7.8, 1H); 7.57 (*t*, *J* = 7.5, 1H); 7.79 (*t*, *J* = 7.5, 1 H); 7.79 (*d*, *J* = 7.8, 1H).

^{13}C NMR: 173.34; 137.30; 134.00; 133.95; 129.56; 124.21; 121.65; 84.08; 69.76; 60.28; 55.45; 41.02; 25.66 (3C); 20.97; 18.25; 17.91; 14.41; -4.34; -5.07.

MS: 426 (0.16, $[C_{21}H_{35}NSO_5Si\text{-}CH_3]^+$); 384 (17); 352 (8); 340 (2); 272 (18) 240 (14); 173 (14); 159 (25); 115 (16); 103 (31); 99 (24); 89 (42); 73 (100); 59 (25).

HR-MS: 384.1306 ($[C_{21}H_{35}NSO_5Si\text{-}C(CH_3)_3]^+$; calc. 384.1294).

4(*R*)-Methoxy-3(*R*),5(*R*)-dimethyl-dihydro-furan-2-one (16)

A solution of **24** (130 mg, 0.29 mmol) in CH_3CN (3ml) was treated at r.t. in a polypropylene vessel with 0.15 ml of 40 % aq. hydrofluoric acid. The reaction was monitored by TLC and GC and shown to be complete in < 1 h. The reaction mixture was diluted with CH_2Cl_2 and then washed with sat. aq. $NaHCO_3$. Drying over Na_2SO_4 and careful removal of the solvent by distillation gave the crude product which was purified by FC (pentane:Et_2O 4:1). The lactone eluted as the initial product (32mg, 75%). GC (99.8%), ret. time 2.43 min. $[\alpha]_D$ = +29.2; $[\alpha]_{578}$ = +30.7; $[\alpha]_{546}$ = +34.6; $[\alpha]_{436}$ = +50.7; $[\alpha]_{365}$ = +65.4 (c = 0.13). The spectral data were identical to those of the sample of **16** obtained from degradation of the natural product.

Anal. calc. for $C_7H_{12}O_3$: C, 58.32; H, 8.39. Found: C, 58.38; H, 8.42.

2(*S*)-Hydroxy-3(*R*)-methyl-succinic acid dimethyl ester (26)

n-Butyllithium (1.44 M in hexane, 47.1 ml, 67.8 mmol) was added to a solution of diisopropylamine (11.5 ml, 81.3 mmol) in THF (110 ml) at 0 °C. The reaction was stirred 20 min at 0 °C then cooled to -78 °C. Dimethyl (*S*)-malate (5.00 g, 30.8 mmol) was added over 1 min as a solution in THF (10 ml) and stirring was continued 1 h at -78 °C. Methyl iodide (5.23 ml, 83.8 mmol) was added over 1 min and the resulting mixture was stirred 18 h at -78 °C. The reaction was quenched by the addition of acetic acid (6.3 ml, 109 mmol) in Et_2O (10 ml) and allowed to warm to r.t. The mixture was poured onto sat. aq. NH_4Cl soln., which was extracted (3x) with EtOAc. The combined organic layers were washed with sat. aq. NaCl soln., dried ($MgSO_4$) and concentrated. FC (hexane/Et_2O 2:3) gave the product **26** (3.56 g, 66%) as a 91:9 mixture of Me-epimers, obtained as a pale yellow oil. $[\alpha]_D$ = -4.1 {lit.[21] $[\alpha]_D$ = -4.1 (c = 1.035 in Et_2O)}; $[\alpha]_{578}$ = -4.4; $[\alpha]_{546}$ = -4.6; $[\alpha]_{436}$ = -5.4; $[\alpha]_{365}$ = -3.0 (c = 1.0 in Et_2O).
IR: 3500 br, 2950, 1735, 1440, 1210, 1140, 1100, 1070, 1010.
^{1}H NMR (major isomer): 1.31 (*d*, *J* = 7.5, 3 H); 3.02-3.08 (*m*, 1 H); 3.15 (*d*, *J* = 6.5, 1 H); 3.70 (*s*, 3 H); 3.81 (*s*, 3 H); 4.28 (*dd*, *J* = 6.5, 3.5, 1 H).
^{13}C NMR: 173.66 (*s*); 173.37 (*s*); 72.49 (*d*); 52.70 (*q*); 51.99 (*q*); 43.17 (*d*); 13.09 (*q*).
MS: 177 (2, $[C_7H_{12}O_5+H]^+$); 145 (17); 117 (95); 85 (100); 57 (75).
HR-MS: 177.0779 ($[C_7H_{12}O_5+H]^+$; calc. 177.0763).

2(*S*)-(2,2-Diethyl-[1,3]dioxolan-4(*S*)-yl)-propan-1-ol (30)

Pyridinium *p*-toluenesulfonate (0.10 g, 0.4 mmol) was added to a stirred solution of **26** (3.56 g, 20.2 mmol) and dihydropyran (2.75 ml, 30.3 mmol) in CH_2Cl_2 (40 ml). After 18 h, the solution was washed with sat. aq. NaCl soln., dried ($MgSO_4$) and concentrated to give **27** as a yellow oil (5.47 g). The crude product was added as a solution in Et_2O (20 ml) to a stirred suspension of lithium aluminium hydride (1.54 g, 40.4 mmol) in Et_2O (60 ml) at 0 °C. The mixture was stirred 30 min at 0 °C then allowed to warm to r.t. and stirred 18 h at this temperature. EtOAc (15 ml) was added slowly to the mixture followed by sodium sulfate decahydrate (*ca.* 20 g). After stirring vigorously for 3 h the mixture was filtered through Celite and concentrated to give **28** as a yellow oil (4.33 g). The crude product was dissolved in MeOH (100 ml) to which was added Amberlite IR-120 (0.20 g). The mixture was stirred 18 h at r.t. then filtered and concentrated. Toluene was added and removed under reduced pressure (3x) leaving **29** as a colourless oil (2.78 g). The crude product was dissolved in a mixture of 3-pentanone (25 ml) and THF (50 ml). *p*-Toluenesulphonic acid (0.10 g, 0.53 mmol) was added and the mixture was heated at reflux for 18 h. The reaction was neutralised by the addition of solid Na_2CO_3, filtered and concentrated. FC (CH_2Cl_2/Et_2O 6:1) gave the product **30** (1.92 g, 56% from **26**) as a pale yellow oil. $[\alpha]_D$ = +17.8; $[\alpha]_{578}$ = +18.9; $[\alpha]_{546}$ = +21.3; $[\alpha]_{436}$ = +36.2; $[\alpha]_{365}$ = +56.6 (c = 0.5).
IR: 3440 br, 2970, 2940, 2880, 1460, 1200, 1170, 1130, 1080, 1040, 920.
^{1}H NMR: 0.81 (*d*, *J* = 7, 3 H); 0.89 (*t*, *J* = 7.5, 3 H); 0.91 (*t*, *J* = 7.5, 3 H); 1.58-1.70 (*m*, 4 H); 1.79-1.91 (*m*, 1 H); 2.94 (*br d*, *J* = 6.5, 1 H); 3.57-3.71 (*m*, 3 H); 3.93 (*dt*, *J* = 6.5, 8.5, 1 H); 4.12 (*dd*, *J* = 8, 6, 1 H).
^{13}C NMR (50 MHz): 113.37 (*s*); 81.29 (*d*); 69.55 (*t*); 67.75 (*t*); 39.21 (*d*); 29.86 (*t*); 29.53 (*t*); 12.94 (*q*); 8.14 (*q*); 8.03 (*q*).
MS: 159 (48, $[C_{10}H_{20}O_3-C_2H_5]^+$); 129 (8); 100 (18); 85 (100); 75 (20); 67 (13); 57 (98).
HR-MS: 159.1015 ($[C_{10}H_{20}O_3-C_2H_5]^+$, calc. 159.1021).

Toluene-4 -sulphonic acid 2(*R*)-(2,2-diethyl-[1,3]-dioxolan-4(*S*)-yl)-propyl ester (31)

p-Toluenesulphonyl chloride (3.89 g, 20.4 mmol) was added to a stirred solution of the alcohol **30** (1.92 g, 10.2 mmol) in pyridine (15 ml) at 0 °C. The solution was allowed to warm to r.t. and stirring was continued. After 18 h, the mixture was poured onto water, which was extracted (3x) with Et_2O. The combined organic layers were washed with sat. aq. $NaHCO_3$ soln., sat. aq. NaCl soln., dried ($MgSO_4$) and concentrated. FC

(hexane/Et_2O 2:1) gave the tosylate **31** (3.04 g, 87%) as a colourless oil. $[\alpha]_D$ = -11.4; $[\alpha]_{578}$ = -12.1; $[\alpha]_{546}$ = -13.7; $[\alpha]_{436}$ = -22.8; $[\alpha]_{365}$ = -34.4 (c = 0.6).
IR: 2970, 2940, 2880, 1600, 1460, 1360, 1190, 1180, 1080, 970, 940, 920, 810, 670, 560.
^{1}H NMR: 0.81 (*t*, *J* = 7.5, 3 H); 0.83 (*t*, *J* = 7.5, 3 H); 0.90 (*d*, *J* = 7, 3 H); 1.49-1.58 (*m*, 4 H); 1.84-1.95 (*m*, 1 H); 2.45 (*s*, 3 H); 3.53 (*t*, *J* = 7.5, 3 H); 3.79-3.85 (*m*, 1 H); 3.98-4.04 (*m*, 2 H); 4.18 (*dd*, *J* = 9, 3.5, 1 H); 7.34 (*d*, *J* = 8, 1 H); 7.80 (*d*, *J* = 8.5, 1 H).
^{13}C NMR (50 MHz): 144.66 (*s*); 132.96 (*s*); 129.78 (*d*); 113.05 (*s*); 76.59 (*d*); 72.45 (*t*); 68.49 (*t*); 37.25 (*q*); 29.70 (*t*); 29.36 (*t*); 21.63 (*q*); 12.91 (*q*); 8.13 (*q*); 7.91 (*q*).
MS: 315 (7); 314 (17); 313 (100, $[C_{17}H_{26}O_5S\text{-}C_2H_5]^+$); 155 (69); 91 (31).
HR-MS: 313.1112 ($[C_{17}H_{26}O_5S\text{-}C_2H_5]^+$, calc. 313.1109).

2,2-Diethyl-4(*S*)-(2-iodo-1(*R*)-methyl-ethyl)-[1,3]dioxolane (32)

A mixture of the tosylate **31** (2.42 g, 7.08 mmol) and sodium iodide (3.18 g, 21.2 mmol) in acetone (30 ml) was heated at reflux for 18 h. The mixture was poured onto water, which was extracted (3x) with EtOAc. The combined organic layers were washed with 10% aq. sodium thiosulphate, sat. aq. NaCl soln., dried ($MgSO_4$) and concentrated. Rapid FC (hexane/Et_2O 4:1) gave the iodide **32** (1.94 g, 92 %) as a colourless liquid. $[\alpha]_D$ = -8.2; $[\alpha]_{578}$ = -9.0; $[\alpha]_{546}$ = -10.2; $[\alpha]_{436}$ = -15.2; $[\alpha]_{365}$ = -16.8 (c = 0.6).
IR: 2970, 2940, 2880, 1460, 1380, 1360, 1270, 1200, 1170, 1130, 1080, 920.
^{1}H NMR: 0.89 (*t*, *J* = 7.5, 3 H); 0.90 (*t*, *J* = 7.5, 3 H); 0.92 (*d*, *J* = 6.5, 3 H); 1.46-1.55 (*m*, 1 H); 1.58-1.66 (*m*, 4 H); 3.33 (*dd*, *J* = 9.5, 6.5, 1 H); 3.45 (*dd*, *J* = 9.5, 3.5, 1 H); 3.59 (*t*, *J* = 8, 1 H); 3.77-3.83 (*m*, 1 H); 4.07 (*dd*, *J* = 7.5, 6, 1 H).
^{13}C NMR: 113.07 (*s*); 79.29 (*d*); 68.57 (*t*); 38.72 (*d*); 29.93 (*t*); 29.63 (*t*); 17.00 (*q*); 14.11 (*t*); 8.18 (*q*); 7.94 (*q*).
MS: 270 (9); 269 (100, $[C_{10}H_{19}IO_2\text{-}C_2H_5]^+$); 195 (54); 68 (28); 67 (21); 57 (100).

6(*S*)-(2,2-Diethyl-[1,3]dioxolan-4(*S*)-yl)-3-oxo-heptanoic acid methyl ester (34)

n-Butyllithium solution (1.6 M in hexane, 5.67 ml, 9.07 mmol) was added to a stirred solution of diisopropylamine (1.57 ml, 11.09 mmol) in THF (10 ml) at 0 °C. After 20 min the solution was cooled to -25 °C and methyl acetoacetate (**33**, 0.435 ml, 4.03 mmol) was added. The reaction was warmed to 0 °C and stirred at this temperature for 30 min, when HMPA (5 ml) was added. After 5 min, the iodide **32** (1.00 g, 3.36 mmol) was added as a solution in THF (5 ml) and stirring was continued at 0 °C. After 2.5 h the reaction was quenched by the addition of sat. aq. NH_4Cl soln.. Work-up (EtOAc/sat. aq. NH_4Cl soln.) and FC (hexane/Et_2O 2:1) gave the product **34** (0.71 g, 74%) as a colourless oil. $[\alpha]_D$ = +12.6; $[\alpha]_{578}$ = +13.4; $[\alpha]_{546}$ = +15.9; $[\alpha]_{436}$ = +27.9; $[\alpha]_{365}$ = +50.4 (c = 0.4).
IR: 2970, 2940, 2880, 1749, 1717, 1460, 1440, 1320, 1160, 1080, 920.
^{1}H NMR: 0.82 (*d*, *J* = 6.5, 3 H); 0.87 (*t*, *J* = 7.5, 3 H); 0.89 (*t*, *J* = 7.5, 3 H); 1.48-1.65 (*m*, 2 H); 1.60 (*q*, *J* = 7.5, 4 H); 1.84-1.94 (*m*, 1 H); 2.58-2.72 (*m*, 2 H); 3.46 (*s*, 2 H); 3.51 (*t*, *J* = 8, 1 H); 3.73 (*s*, 3 H); 3.73-3.82 (*m*, 1 H); 4.01 (*dd*, *J* = 7.5, 6, 1 H).
^{13}C NMR(50 MHz): 202.66 (*s*); 167.68 (*s*); 112.74 (*s*); 80.67 (*d*); 68.83 (*t*); 52.28 (*q*); 48.98 (*t*); 40.67 (*t*); 36.17 (*d*); 29.89 (*t*); 29.63 (*t*); 27.84 (*t*); 15.51 (*q*); 8.22 (*q*); 7.97 (*q*).
MS: 257 (10, $[C_{15}H_{26}O_5\text{-}C_2H_5]^+$); 183 (8); 165 (10); 151 (12); 109 (34); 105 (37); 81 (25); 57 (100).
HR-MS: 257.1392 ($[C_{15}H_{26}O_5\text{-}C_2H_5]^+$, calc. 257.1389).

1(*S*)-(2(*S*)-Methyl-6,8-dioxa-bicyclo[3.2.1]oct-5(*R*)-yl)-acetic acid methyl ester (35)

A solution of the β-keto ester **34** (1.12 g, 3.92 mmol) and *p*-toluenesulphonic acid (0.074 g, 0.39 mmol) in CH_2Cl_2 (20 ml) was heated at reflux for 18 h. The solution was then cooled to r.t., washed with satd. aq. $NaHCO_3$ soln., dried ($MgSO_4$) and concentrated. FC (hexane/Et_2O 2:1) gave the product **35** (0.685 g, 87%) as a colourless oil. $[\alpha]_D$ = -67.7; $[\alpha]_{578}$ = -70.6; $[\alpha]_{546}$ = -80.1; $[\alpha]_{436}$ = -135.0; $[\alpha]_{365}$ = -209.3 (c = 1.2).
IR: 2950, 2890, 1743, 1460, 1440, 1370, 1350, 1220, 1170,1050, 1000.

^{1}H NMR: 1.15 (*d*, *J* = 7, 3 H); 1.34 (*ddq*, *J* = 13.5, 5.5, 1.5, 1 H); 1.63-1.73 (*m*, 2 H); 1.87 (*dt*, *J* = 5.5, 13.5, 1 H); 2.00-2.11 (*m*, 1 H); 2.77 (*s*, 2 H); 3.72 (*s*, 3 H); 3.88-3.94 (*m*, 2 H); 4.31 (*br d*, *J* = 4.5, 1 H).
^{13}C NMR: 169.54 (*s*); 106.45 (*s*); 79.61 (*t*); 69.78 (*t*); 51.88 (*d*); 43.21 (*t*); 31.40 (*d*); 30.42 (*t*); 22.93 (*t*); 17.14 (*q*).
MS: 201 (62, $[C_{10}H_{16}O_4+H]^+$); 200 (9); 183 (10); 169 (13); 101 (70); 71 (100); 54 (56).
HR-MS: 200.1044 ($[C_{10}H_{16}O_4+H]^+$, calc. 200.1049).

(6(*S*)-Hydroxymethyl-5(*S*)-methyl)-tetrahydropyran-2(*R*)-yl) acetic acid methyl ester (36)

Triethylsilane (1.53 ml, 9.62 mmol) and titanium tetrachloride solution (1 M in CH_2Cl_2, 2.89 ml, 2.89 mmol) were added to a stirred, -78 °C solution of **35** (0.481 g, 2.41 mmol) in CH_2Cl_2 (10 ml). After stirring 1 h at -78 °C the temperature was allowed to rise to -25 °C over 90 min. The reaction was then quenched by the addition of water. Work-up (CH_2Cl_2/H_2O) and FC (hexane/Et_2O 1:4) gave the alcohol **36** (0.345 g, 71%) as a colourless oil. $[\alpha]_D$ = +9.4; $[\alpha]_{578}$ = +10.1; $[\alpha]_{546}$ = +11.7; $[\alpha]_{436}$ = +20.8; $[\alpha]_{365}$ = +34.0.
IR: 3470 br, 2930, 2870, 1740, 1440, 1200, 1090, 1020.
^{1}H NMR: 0.83 (*d*, *J* = 6.5, 3 H); 1.20-1.51 (*m*, 3 H); 1.66-1.71 (*m*, 1 H); 1.76-1.83 (*m*, 1 H); 2.16 (*br dd*, *J* = 7.5, 4, 1 H); 2.43 (*dd*, *J* = 15, 5, 1 H); 2.56 (*dd*, *J* = 15, 7.5, 1 H); 3.12 (*ddd*, *J* = 9.5, 7, 3, 1 H); 3.51 (*br ddd*, *J* = 11, 8, 3.5, 1 H); 3.69 (*s*, 3 H); 3.71-3.82 (*m*, 2 H).
^{13}C NMR:171.57 (*s*);83.56 (*d*); 74.05 (*d*); 63.82 (*t*); 51.55 (*q*); 41.22 (*t*); 32.23 (*t*); 31.61 (*t*); 31.21 (*d*);17.05 (*q*).
MS: 203 (1, $[C_{10}H_{18}O_4+H]^+$); 184 (4); 171 (61); 139 (58); 97 (56); 59 (100); 55 (85).
Anal. calc. for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found: C, 59.21; H, 8.97.

(6(*S*)-Formyl-5(*S*)-methyl)-tetrahydropyran-2(*R*)-yl) acetic acid methyl ester (37)

DMSO (0.173 ml, 2.44 mmol) was added to a stirred, -78 °C solution of oxalyl chloride (0.105 ml, 1.22 mmol) in CH_2Cl_2 (4 ml). After 10 min a solution of the alcohol **36** (0.164 g, 0.81 mmol) in CH_2Cl_2 (2 ml) was added dropwise and the mixture was stirred 15 min at -78 °C. Triethylamine (0.85 ml, 6.09 mmol) was added slowly and the mixture was allowed to warm to r.t. over 1 h, and then quenched by the addition of sat. aq. NH_4Cl soln.. Work-up (CH_2Cl_2/sat. aq. NH_4Cl soln.) and FC (hexane/Et_2O 1:1) gave the aldehyde **37** (0.142 g, 87%) as a colourless oil. $[\alpha]_D$ = -61.6; $[\alpha]_{578}$ = -65.1; $[\alpha]_{546}$ = -76.9; $[\alpha]_{436}$ = -173.1; $[\alpha]_{365}$ = -488.7 (c = 0.5).
IR: 2930, 1739, 1440, 1200, 1090, 1020, 860.
^{1}H NMR: 0.93 (*d*, *J* = 6.5, 3 H); 1.25-1.46 (*m*, 2 H); 1.54-1.65 (*m*, 1 H); 1.69-1.76 (*m*, 1 H); 1.88-1.95 (*m*, 1 H); 2.47 (*dd*, *J* = 15.5, 5.5, 1 H); 2.63 (*dd*, *J* = 15.5, 7.5, 1 H); 3.43 (*dd*, *J* = 10.5, 2.5, 1 H); 3.69 (*s*, 3 H); 3.80-3.87 (*m*, 1 H); 9.53 (*d*, *J* = 2.5, 1 H).
^{13}C NMR (50 MHz): 200.62 (*d*); 171.43 (*q*); 86.70 (*d*); 73.56 (*d*); 51.69 (*q*); 40.94 (*t*); 32.12 (*t*); 30.83 (*t*); 30.52 (*d*); 16.36 (*q*).
MS: 201 (12, $[C_{10}H_{16}O_4+H]^+$); 183 (10); 171 (83); 139 (82); 111 (45); 97 (100); 55 (95).

[6(*S*)-Acetyl-5(*S*)-methyl-tetrahydropyran-2(*R*)-yl]-acetic acid methyl ester (4)

Methylmagnesium bromide solution (3 M in Et_2O, 0.197 ml, 0.59 mmol) was added dropwise to a stirred solution of the aldehyde **37** (0.099 g, 0.495 mmol) in Et_2O (3 ml) at -78 °C. The mixture was allowed to warm to -40 °C over 30 min then stirred 1 h at this temperature. The mixture was quenched by the addition of water and diluted with Et_2O. Washing with 2% aq. HCl, drying ($MgSO_4$) and concentration gave a colourless oil (0.093 g). This was dissolved in acetone (5 ml) and to this stirred solution was added Jones' reagent solution until an orange colour persisted. Stirring was continued 20 min at r.t., when water (20 ml) was added and the acetone was removed under reduced pressure. The aq. mixture was extracted (3x) with Et_2O and the combined organic layers were washed with sat. aq. $NaHCO_3$ soln., sat. aq. NaCl soln., and then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by FC (hexane/Et_2O 2:1) gave the ketone **4** (0.068 g, 64% from **37**) as a colourless oil. $[\alpha]_D$ = -94.6; $[\alpha]_{578}$ = -99.9; $[\alpha]_{546}$ = -117.7; $[\alpha]_{436}$ = -252.8; $[\alpha]_{365}$ = -608.0 (c = 1.5).
Anal. calc. for $C_{11}H_{18}O_4$: C,61.66; H, 8.47. Found: C, 61.54; H, 8.54. The spectral data properties were identical to those of the sample of **4** obtained from the natural product.

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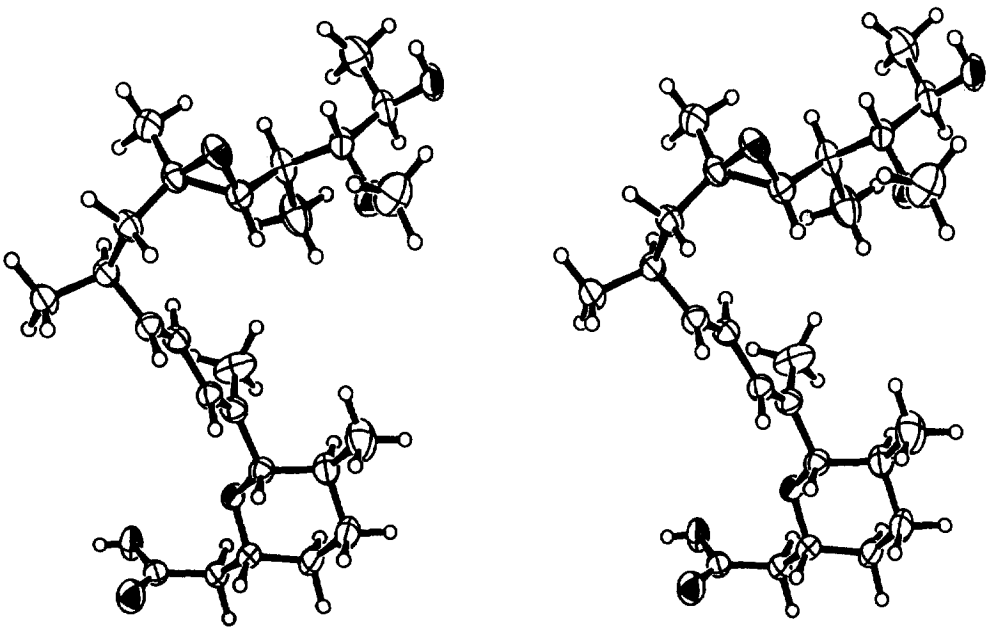
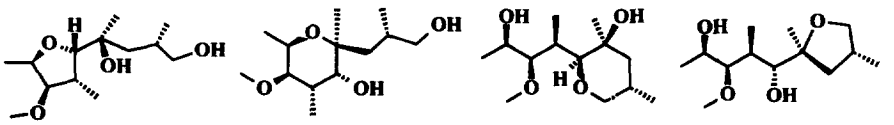
4. Details of the X-ray structure will be published elsewhere; Le-Van, N.; Weber, H. P.; Trueb. W.; Sanglier, J. J., *J. Antibiotics*, in preparation.
5. Lists of refined co-ordinates have been submitted to the editor for deposition at the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. A stereoview of the molecule is shown below.



ORTEP stereo drawing of the crystalline conformation of herboxidiene. The 50% probability ellipsoids of the anisotropic atomic thermal vibration is shown for C- and O-atoms. H-atoms have been given a constant radius of 0.10 A. Oxygen atoms are shaded.

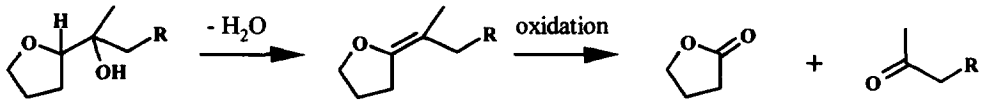
6. Several regioisomers are possible, *viz:*



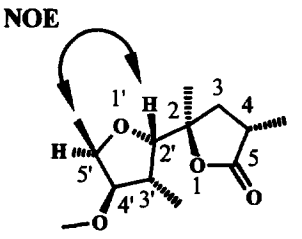
A **B** **C** **D**

Acetylation led to a diacetate as shown by ^{1}H NMR ruling out structures **A** and **C** which contain tertiary alcohol functions. The signals for the protons adjacent to the hydroxy groups were shifted downfield to 5.09 and 4.90 ppm through acetylation. The signal at 5.05 ppm (1H) was a quintet (J = 6.6 Hz) which was assigned to the H-18 proton (herboxidiene numbering) while the signal at 4.90 ppm (1H) was a doublet (J = 7.6 Hz) which requires that **D** is the compound that was formed. The stereochemistry for the epoxide opening is assumed and not confirmed.

7. Large scale fermentation of herboxidiene and subsequent purification also lead to isolation of the corresponding acid of **7**. As we had multigram amounts of this compound (readily converted to the methyl ester using the procedure for that of herboxidiene) we were very keen to find a use for as much of the molecule as possible.
8. Full details of the reactions of herboxidiene under acidic conditions will be reported shortly.
9. The stereochemistry of the epoxide ring opening was not reported by Isaac *et al.*[1] The stereochemistry indicated for this molecule is based upon the experiment discussed in note 12.
10. No evidence for oxidation at C8-C9 was observed by examination of crude NMR mixtures and analysis of the product profile after diol cleavage.
11. Baskaran, S.; Chandrasekaran, S. *Tetrahedron Lett.* **1990**, 31, 2775. The reaction presumably proceeds by elimination of water and subsequent oxidative cleavage of an intermediate enol ether, *viz*:



12. It is interesting to note that this cleavage procedure would have enabled determination of the relative and absolute configuration of herboxidiene even if the crystal structure had not been available as the synthesis of the appropriate alcohol required for oxidation to **17** is reported in the literature. See; Grieco, P. A.; Hon, Y.S; Perez-Medrano, A. *J. Am. Chem. Soc.* **1988**, 110, 1630.
13. The bicyclic lactone **19** was analysed by 2D ROESY NMR to determine the stereochemistry of the epoxide ring opening in herboxidiene. The most relevant NOE was that observed between H-2' and CH_3-5' while, conversely, no NOE was observed between H-2' and H-5'.



19

Surprisingly, no NOE was observed for the CH_3-4 and CH_3-2 protons. However, as the stereochemistry at C-2 (respectively C-14 in herboxidiene) should remain unchanged independent of whether the epoxide opens under S_N2 or S_N1 conditions, the observed NOE for the H-2' proton in **19** strongly suggests that epoxide opening in herboxidiene by the 18-OH functionality occurs with inversion of configuration. An authentic sample of the lactone **19** was also prepared by Ley oxidation [(tetrapropylammonium peruthenate (5% mol)/ N-methyl-morpholine oxide (1.5 eq.) /CH_2Cl_2, 0 °C to r.t.)] of **13** in 94% yield.

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18. The *syn-syn* stereochemistry was unambiguously confirmed by NMR analysis of the acetonide derived from the aldol adduct as described in reference 16. The high selectivity obtained even though the substrates are "mismatched" shows that the reaction proceeds with a very high level of reagent control.
19. As evidenced by NMR analysis of **22**, and GC analysis of the tris-TES ether of the triol obtained by reduction with $LiAlH_4$. See reference 16.
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