Pigments of fungi. Part 41.[1,2] Synthesis of (*S*)-(+)- and (±)-dermolactone; stereochemistry of dermolactone from the Australian fungus *Dermocybe sanguinea* (Wulf. ex Fr.) Wünsche sensu Cleland

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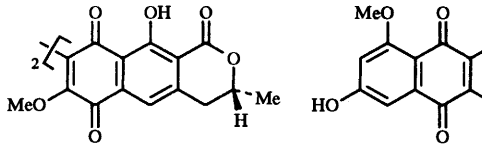
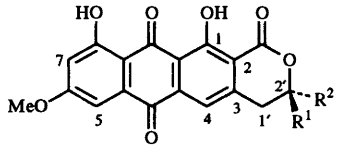
(*S*)-(+)-Dermolactone **3** has been synthesised in monochiral form beginning with ethyl (*S*)-lactate, the tetracyclic nucleus being assembled by way of a regiospecific cycloaddition between the known chloronaphthoquinone **15** and the novel, highly functionalised chiral butadiene derivative **5**. Isochiral dermolactone **3** + **4** is prepared in the same way from (±)-**5**. Dermolactone, as it occurs naturally, is shown by ^{1}H NMR shift experiments on the corresponding permethyl ethers **25** and **27**, using [Eu(+)-(hfc)$_3$], to consist of an anisochiral mixture of the (*S*)-(+)- and (*R*)-(−)-enantiomers **3** and **4**, respectively, in which the former predominates in the ratio of 1.8:1 (28.6% ee).

Although naphthoquinones bearing a terminal δ-lactone ring, *e.g.* xanthomegnin **1** and its relatives, form an important group within the benzoisochromanquinone class of naturally occurring pigments,[3] analogues in the anthraquinone series are extremely rare. Thus, only anhydroleprolutein **2**, a trace constituent of several toadstools from the subgenus *Leprocybe* of *Cortinarius*,[4] and dermolactone **3** and/or **4**[5] and its 4-hydroxy derivative,† have been reported to date. (+)-Dermolactone is the major orange pigment present in the fruit bodies of the Australian toadstool *Dermocybe sanguinea* (sensu Cleland), where it occurs along with several dihydroanthracenones and anthraquinones with which it shares a nonaketide origin.[5]



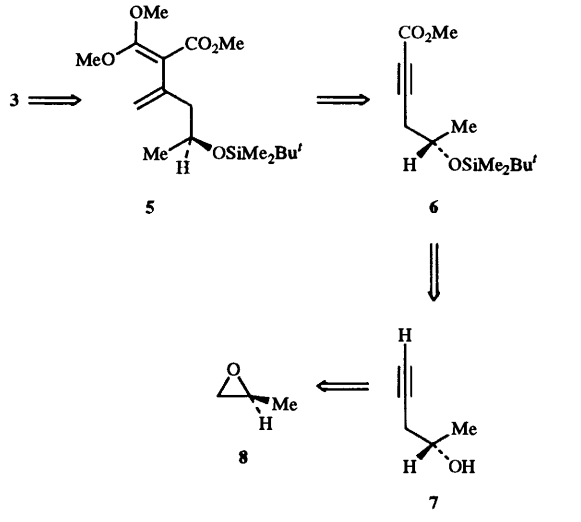
1 **2**



3 R^1 = Me, R^2 = H
4 R^1 = H, R^2 = Me

The absolute configuration at the stereogenic centre(s) in naphthoquinone lactones of the xanthomegnin type was determined as *R* by chemical correlation with (*R*)-β-hydroxybutyric acid.[6] Unfortunately, a similar approach to solving the stereochemical question in the case of dermolactone **3** or **4** is precluded by the scarcity of the natural product. Consequently, we have developed a synthesis of dermolactone in both the isochiral **3** + **4** and monochiral **3** forms,[7] whereupon chiroptical and spectroscopic comparison between the natural and synthetic materials has revealed the stereochemical composition of the naturally occurring pigment.

† For consistency and comparison between spectroscopic data we have numbered the anthraquinone nucleus as shown in the formula for quinone **3**. The IUPAC names for all quinones are given in the Experimental section.

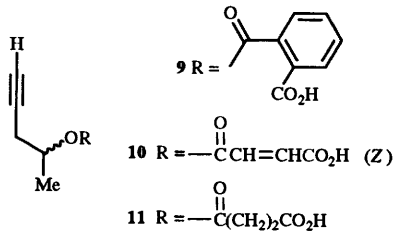


Scheme 1

Results and discussion

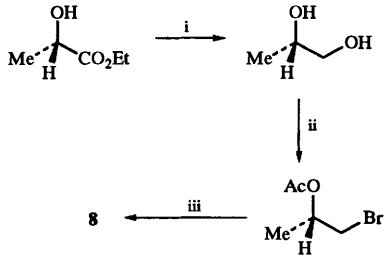
In an earlier part of this series[8] we showed that highly functionalised butadiene derivatives bearing a side chain containing a protected secondary hydroxy group are available in monochiral form by reaction between ketene dimethyl acetal and the appropriate chiral propiolate ester, in an extension of Brannock's protocol.[9] Furthermore, we established that complex dienes so formed undergo efficient Diels–Alder cycloaddition with naphthoquinone dienophiles to yield anthraquinones in which the stereogenic side chain is retained intact. Application of this methodology to the synthesis of (*S*)-dermolactone **3** is shown in retrosynthetic terms in Scheme 1. It requires the hitherto unknown chiral diene **5**, which should be available by reaction of ketene dimethyl acetal with the propiolate ester **6**. In turn, we reasoned that the ester **6** could be obtained from (*S*)-pent-4-yn-2-ol **7**, the latter having been made previously from (*S*)-propylene oxide **8**.[10] Alternatively, **7** would become available more economically if a successful resolution of the commercial isochiral mixture could be developed.

Accordingly, and encouraged by our success in resolving (±)-but-3-yn-2-ol,[8] we prepared the phthalate half ester **9** of (±)-**7**. Subsequent reaction of the phthalate **9** with (*S*)-1-phenylethylamine and with (−)-brucine gave, in both cases, nicely crystalline salts (1:1 mixtures of diastereoisomers by



^{1}H NMR spectroscopy) that, unfortunately, could not be fractionated even by repeated recrystallisation. Equally disappointing were similar attempts to resolve (±)-**7** *via* the crystalline maleate **10** and succinate **11** half esters.

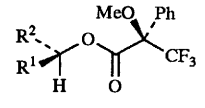
Consequently, we turned to the synthesis of **7**. (*S*)-Propylene oxide **8** was prepared by Golding's procedure from ethyl (*S*)-lactate according to the reactions depicted in Scheme 2.[11]



Scheme 2 *Reagents:* i, $LiAlH_4$; ii, 33% HBr in AcOH; iii, $C_5H_{11}ONa$, $C_5H_{11}OH$

Subsequently, reaction between **8** and the ethylenediamine complex of lithium acetylide[12] gave (*S*)-pent-4-yn-2-ol **7** in ≥98% ee, and 40% yield over the four steps.

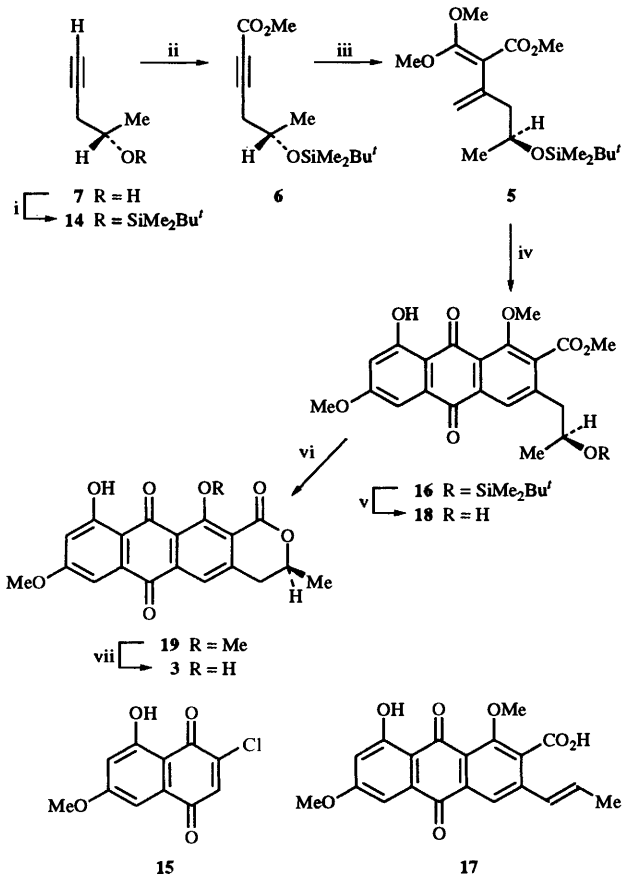
Mosher ester formation was used to assay the enantiomeric purity of the chiral alcohol **7**.[13] Thus, with (±)-**7** and (*R*)-α-methoxy-α-trifluoromethylphenylacetic acid, a mixture of the diastereoisomeric esters **12** and **13** was obtained in 90% yield.



12 R^1 = Me, R^2 = HC≡CCH$_2$—
13 R^1 = HC≡CCH$_2$—, R^2 = Me

As expected, the ^{1}H NMR spectrum of this mixture displayed discrete resonances for each diastereoisomer. Particularly diagnostic were the signals assignable to the *C*-methyl and prop-2-ynylic methylene protons.[13,14] Thus, the methyl protons of **12**, the ester derived from the (*S*)-alcohol **7**, resonate as a doublet at δ 1.45, while the diastereotopic methylene protons resonate, each as a double doublet of doublets, at δ 2.48 and 2.52, respectively. Alternatively, the methyl protons of the ester **13** appear as a doublet at δ 1.35, with the methylene protons coincident as double doublets at δ 2.56. Esterification of the optically active pentynol **7** with the (*R*)-Mosher acid gave the ester **12** as the only product detectable by ^{1}H NMR spectroscopy.

The seven steps between (*S*)-pent-4-yn-2-ol **7** and (*S*)-dermolactone **3** are summarised in Scheme 3. Thus, silylation of **7** (93% yield), metallation of the resulting silyl ether **14**, and reaction of the acetylide so formed with ethyl chloroformate, gave the (*S*)-acetylenic ester **6** in 82% yield from **14**. The diene **5** was obtained in 89% yield by heating the ester **6** with ketene dimethyl acetal for 24 h in a sealed tube at 165 °C, followed by distillation directly from the reaction mixture. The diene **5**, $[\alpha]_D^{22}$ +23.5, exhibits characteristic olefinic proton resonances at δ 5.10 and 4.90, and methoxy singlets at δ 3.84, 3.70 and 3.69



15 **17**

Scheme 3 *Reagents:* i, Bu^tMe_2SiCl, imidazole, DMF; ii, BuLi, MeO_2CCl; iii, $H_2CC(OMe)_2$, 165 °C; iv, 2-chloro-8-hydroxy-6-methoxy-1,4-naphthoquinone **15**, 160 °C; v, aq. H_2SO_4, THF; vi, *p*-TsOH, CH_2Cl_2; vii, 1 equiv. BCl_3, CH_2Cl_2

in the ^{1}H NMR spectrum. Signals from the side chain protons (see Experimental section) are in full accord with the structure **5**.

Cycloaddition between the diene **5** and 2-chloro-8-hydroxy-6-methoxy-1,4-naphthoquinone **15** took place efficiently in a sealed flask, without solvent, at 160 °C during 4 h. After chromatography over silica gel and crystallisation, the anthraquinone **16**, $[\alpha]_D^{22}$ −32.5 was obtained in 69% yield. The spectroscopic data are in full accord with the structure **16**. Thus, the ^{1}H NMR spectrum shows a chelated hydroxy resonance at δ 13.14, *meta* coupled doublets at δ 6.73 (7-H) and 7.34 (5-H), and an aromatic singlet at δ 8.03 (4-H), while singlets at δ 3.93, 3.96 and 3.97 arise from the protons of the methyl ether and ester groups. The diastereotopic protons of the side chain methylene group and the C-2′ methine proton resonate as complex multiplets centred at δ 2.76 and 4.08, respectively, while a doublet at δ 1.20 is assigned to the protons of the C-2′ methyl group. Singlets at δ −0.26 (3 H), −0.07 (3 H) and 0.78 (9 H) confirm that the *tert*-butyldimethylsilyloxy group has been retained intact.

The fully proton coupled ^{13}C NMR spectrum of the anthraquinone **16** confirmed that cycloaddition between **5** and **15** had occurred exclusively with the desired, and predicted, regioselectivity. Thus, the C-9 quinone carbonyl carbon of **16** resonates as a sharp singlet at δ 186.1, while the carbon at C-10 appears as a triplet (*J* 5 Hz) at δ 181.8 due to three-bond coupling with the *peri* hydrogens at C-4 and C-5. These observations are consistent only with the substitution pattern depicted in formula **16** and no other anthraquinonoid product could be detected in the product mixture.

In our first attempt to cleave the silyl ether from the side chain of the quinone **16**, the (isochiral) substrate was exposed to

tetrabutylammonium fluoride in tetrahydrofuran.[15] However, the only product obtained after work up and chromatography was the new anthraquinone carboxylic acid **17** (68% yield), which was characterised from the ^{1}H NMR spectrum. Presumably, the alcoholate anion generated on cleavage of the ether (±)-**16** cyclises to form the lactone (±)-**19**, which then suffers loss of a benzylic proton to the strongly basic fluoride ion, to afford the product **17** upon ring opening.

Removal of the silyl ether from **16** without effecting concomitant elimination was achieved by using dilute sulfuric acid in tetrahydrofuran at room temperature. The product obtained in 89% yield, was a mixture of the secondary alcohol **18** and the lactone **19**, which could be separated by chromatography. The ratio of **18**:**19** varied from run to run, but the alcohol **18** could not be induced to lactonise completely under the aqueous conditions. Instead, the mixture of **18** and **19** (or the purified alcohol **18**) was stirred with toluene-*p*-sulfonic acid in dichloromethane to afford the lactone **19** in quantitative yield. The ^{1}H NMR spectrum of **19** shows singlets δ 13.14, 4.12 and 3.94 due to the chelated hydroxy and the C-1 and C-6 methoxy groups, respectively. The diastereotopic methylene protons give rise to a multiplet at δ 3.05 while the C-2′ methine proton appears at δ 4.62, considerably deshielded relative to its counterpart in the secondary alcohol **18** (δ 4.13). In the IR spectrum of **19** a characteristic δ-lactone carbonyl absorption appears at 1728 cm^{-1}.

Finally, selective removal of the sterically encumbered 1-*O*-methyl group from **19** was achieved by using boron trichloride[16] at 0 °C during 1 h to afford (*S*)-dermolactone **3** in quantitative yield. The ^{1}H and ^{13}C NMR, mass and electronic spectra of the (*S*)-anthraquinone **3** proved indistinguishable from data recorded for the natural product,[5] however, there was a serious discrepancy when it came to comparing the specific rotation of the natural and synthetic materials. The specific rotation reported for dermolactone from *D. sanguinea* (sensu Cleland) at 589 nm in chloroform is +22 (*c* 0.07).[5] (*S*)-Dermolactone **3**, on the other hand, shows $[\alpha]_D$ +169.3 (*c* 0.21) in the same solvent. In order to make direct comparison between the monochiral quinone **3** and the natural product we isolated dermolactone afresh from *D. sanguinea* (sensu Cleland) collected from the original site.[5] Extraction and chromatography according to the published procedure, followed by recrystallisation gave dermolactone with $[\alpha]_D$ +45.9 (*c* 0.21). While this figure is significantly higher than that quoted in the literature[5] it remains manifestly anomalous in comparison with the data reported above for the synthetic quinone **3**. To clarify this anomaly we explored the use of ^{1}H NMR spectroscopy in the presence of a chiral shift reagent.

(±)-Dermolactone **3** + **4** was prepared from isochiral pent-4-yn-2-ol (±)-**7** by a route parallel to that depicted in Scheme 3. However, when successive aliquots of tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III) [Eu(+)-(hfc)$_3$] were added to a solution of (±)-dermolactone **3** + **4** in deuteriochloroform, no discernible shifts were observed for any of the signals in the ^{1}H NMR spectrum. An explanation for this lack of coordination between the shift reagent and the quinone could lie in the preexistent strong intramolecular hydrogen bonding between the *peri* hydroxy groups and the quinone and lactone carbonyls. Consequently, we prepared the acetates **20**, **21** and **22**, and the methyl ethers **23** and **24** of (±)-dermolactone by standard methods. Of these derivatives only the (±)-1,8-di-*O*-methyl ether **24** was resolved in the presence of [Eu(+)-(hfc)$_3$]. The ^{1}H NMR spectrum of the ether **24** (0.7 mol dm^{-3} in deuteriochloroform) recorded prior to addition of shift reagent showed three discrete three-proton singlets, at δ 3.97, 3.99 and 4.13 [Fig. 1(*a*)(*i*)], which were assigned to the methoxy groups at C-6, C-8 and C-1, respectively, in **24** from the NOESY spectrum. Addition of [Eu(+)-(hfc)$_3$] (1 mg) caused significant

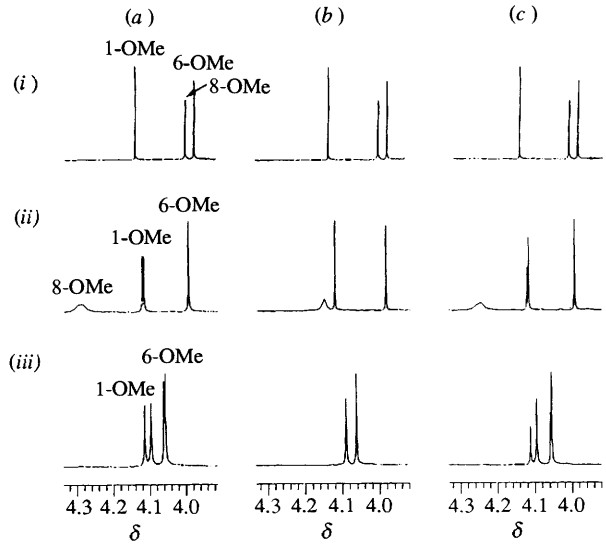
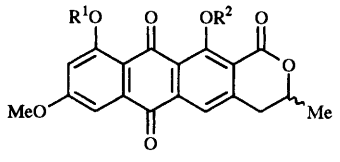
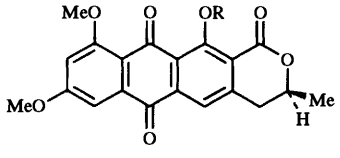


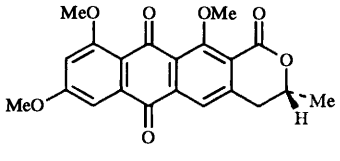
Fig. 1 Partial ^{1}H NMR spectra from chiral shift experiments with the dimethyl ethers of (*a*) (±)-dermolactone **3** + **4**; (*b*) synthetic (*S*)-dermolactone **3** and (*c*) natural dermolactone in the absence (*i*) and in the presence of (*ii*) 1 mg and (*iii*) 3 mg of [Eu(+)-(hfc)$_3$]



20 R^1 = H, R^2 = Ac
21 R^1 = Ac, R^2 = H
22 R^1 = Me, R^2 = Ac
23 R^1 = Me, R^2 = H
24 R^1 = R^2 = Me



25 R = Me
26 R = H



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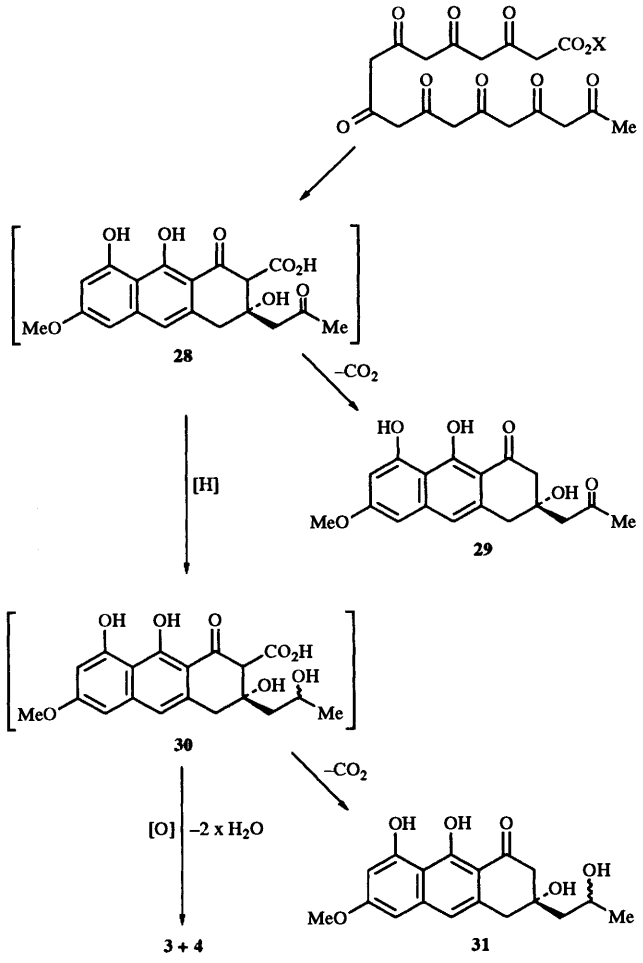
shifts in all three methoxy resonances [Fig. 1(*a*)(*ii*)]. Thus, the signal due to the 6-OMe protons was shifted to lower field by 0.03 ppm and was broadened slightly but not resolved. Similarly, the 8-OMe signal was shifted downfield by 0.29 ppm and suffered considerable broadening. In contrast, the 1-OMe signal was shifted to higher field by 0.01 ppm and was resolved into two equally intense singlets ($\Delta\delta$ 0.006 ppm). When the shift reagent concentration was further increased [Fig. 1(*a*)(*iii*)] the 8-OMe resonance was broadened to obscurity, the 6-OMe signal was shifted downfield and resolved into two equally intense singlets ($\Delta\delta$ 0.004 ppm), while the 1-OMe protons now appeared, shifted slightly further upfield, as a pair of singlets separated by 0.017 ppm. That the component of each pair of singlets which appeared at higher field was due to the methoxy



Scheme 4 Possible biosynthetic relationships between the pigments of *D. sanguinea* sensu Cleland

protons of the (*S*)-1,8-di-*O*-methyl ether **25** was established from the results of shift experiments [Fig. 1(*b*)] involving the dimethyl ether of the synthetic (*S*)-quinone **3**. The partial spectrum shown in Fig. 1(*b*)(*iii*) also adds further testimony to the stereochemical homogeneity of the synthetic quinone **3**.

Finally, we prepared the 1,8-di-*O*-methyl ether of dermolactone as it was isolated by us from *D. sanguinea* (sensu Cleland). The results of shift experiments involving this material are shown in Fig. 1(*c*). Of most significance is the appearance in Fig. 1(*c*)(*iii*) of the components of two pairs of shifted and resolved methoxy signals that, by their unequal intensity, reveal that the naturally derived dimethyl ether must be an anisochiral mixture of **25** and **27**. Integration leads to a ratio of 1.8 to 1 (28.6% de) of the (*S*)-quinone **25** over its stereoisomer **27**, and points, in turn, to the fact that naturally occurring dermolactone is an anisochiral mixture of **3** and **4** in which the (*S*)-enantiomer **3** predominates.

The enantiomeric excess of **3** over **4** in the natural product as determined by the ^{1}H NMR method described above (28.6% ee) is gratifyingly close to that calculated from the respective specific rotation measurements (27.1% ee) discussed earlier.‡

It is difficult to gauge the extent to which anisochiral substances occur in nature, although their presence is well established in certain areas such as animal pheromone chemistry.[17] It is notable in the present context that among *Dermocybe* some dihydroanthracenones occur in anisochiral form,[18] and also that several tetrahydroanthraquinones occur as mixtures of diastereoisomers.[19]

From our earlier labelling studies[5] with *D. sanguinea* (sensu Cleland) it is known that dermolactone **3** + **4**, dermochrysone **29**, and the diastereoisomeric dermochrysonols **31** are derived biosynthetically *via* a putative nonaketide progenitor itself formed, in the usual way, from acetate and malonate (Scheme 4). We deduced the *S* stereochemistry of dermochrysone **29** by comparison of the CD spectrum of the natural product with those of dihydroanthracenones of known chirality and, furthermore, suggested that it arose by decarboxylation of the hypothetical β-keto carboxylic acid **28**. The occurrence of the dermochrysonols **31** as a mixture of diastereoisomers was evident from the ^{1}H NMR spectrum; we assumed at the time that they are epimeric at the side chain stereogenic centre, although the paucity of material precluded a more detailed study. This assumption now finds support in the characterisation of dermolactone as an anisochiral mixture, which is in line with the biogenetic relationships depicted in Scheme 4. Accordingly, we suggest that the side chain carbonyl group in **28** is reduced nonspecifically by one (or specifically to a differing extent by two) enzyme(s) to afford a mixture of diastereoisomeric diols **30**. Decarboxylation of **30** would lead to the known epimers **31**, while aromatisation and lactone formation would afford **3** + **4**. The anisochiral nature of dermolactone may thereby reflect the lack of stereospecificity in going from **28** to **30**.

Experimental

General

Where compounds have been prepared in both isochiral and monochiral forms experimental detail is described only for the optically active series. In such cases, where physical and spectroscopic data of the isochiral products differ from those of their monochiral counterparts, the relevant data for the isochiral compounds are listed in square brackets.§ Melting points were determined on a Kofler hot-stage and are uncorrected. Microanalyses were carried out by Chemical and Microanalytical Services Pty. Ltd., North Essendon, Victoria and National Analytical Laboratories Pty. Ltd., Ferntree Gully, Victoria. Specific rotations were measured using a Perkin-Elmer polarimeter MC241 and are quoted for chloroform solutions, unless stated otherwise, with concentrations (*c*) quoted in g per 100 cm^3 and are given in units of 10^{-1} deg cm^2 g^{-1}. Electronic spectra were recorded on a Varian SuperScan 3 or a Perkin-Elmer Lambda 2 Spectrophotometer using 10 mm quartz cells and ethanolic solutions unless otherwise stated. IR spectra were recorded using a Perkin-Elmer 983G grating spectrophotometer as potassium bromide discs for solids and as films between NaCl plates for liquids. NMR spectra were recorded with JEOL JNM-FX90Q (^{1}H at 90 MHz, ^{13}C at 22.5 MHz), Varian Unity 300 (^{1}H at 300 MHz, ^{13}C at 75 MHz) and JEOL JNM-GX400 (^{1}H at 400 MHz, ^{13}C at 100 MHz) spectrometers. Chemical shifts are quoted on the δ scale, with tetramethylsilane as reference, followed by multiplicity, coupling constant(s) in Hz and assignment. Spectra were obtained as deuteriochloroform solutions unless otherwise specified. Mass spectra were recorded using a V.G. Micromass 7070F instrument at 70 eV or at a lower ionisation potential where specified. The mass of each ion is given followed by its relative abundance. In general, only

‡ Recently, HPLC analysis using a chiral stationary phase (Chiralcel-OD, 25 × 0.46 cm, EtOH, 40 °C) has confirmed a 28% ee of **3** over **4** in natural dermolactone.

§ Such differences in melting point between monochiral and isochiral forms are consistent with the latter crystallising as a 'racemic compound', that is, where antipodes are paired at the level of the unit cell.[20] This phenomenon also leads to differences in the solid state IR spectra that are noted.

peaks with relative abundance of 20% or greater are quoted. In reporting spectral data the following abbreviations have been used: s singlet; d doublet; t triplet; q quartet; m multiplet; p pentet; br broad and sh shoulder.

All cycloadditions were carried out in oven dried glassware that had been previously washed successively with aqueous ammonium carbonate and distilled water.

Materials

All solvents used were redistilled prior to use; tetrahydrofuran and benzene were distilled from potassium benzophenone ketyl under nitrogen immediately prior to use. Dichloromethane was dried by distillation from calcium hydride and stored over 4 Å molecular sieves. Other solvents and reagents were purified by published procedures.[21] Ether refers to diethyl ether and petroleum to the hydrocarbon fraction boiling in the range 40–60 °C. Brine refers to a saturated aqueous sodium chloride.

Column chromatography was performed routinely using Machery Nagel 230–400 mesh (Flash) or Merck Kieselgel 60, 400–560 mesh (short column) silica gel. Preparative thin layer chromatography (PLC) employed Merck Kieselgel GF_{254} or Machery Nagel UV_{254} (20 × 20 cm coated glass plates, 1.0 or 2.0 mm thickness) silica gel. Thin layer chromatography (TLC) was performed using precoated plastic sheets (0.25 mm silica gel as quoted above). Gel permeation chromatography was carried out using 35 × 3 cm columns of Sephadex LH-20 (Pharmacia) suspended and eluted in the solvent(s) as stated.

(±)-Pent-4′-yn-2′-yl hydrogen phthalate 9

A mixture of (±)-pent-4-yn-2-ol (4.0 g, 0.048 mol), freshly crushed phthalic anhydride (7.04 g, 1.0 equiv.) and *N*,*N*-diisopropylethylamine (8.2 cm^3, 1.0 equiv.) in ether (10 cm^3) was stirred overnight at room temperature. The heterogeneous mixture was extracted with saturated aqueous sodium hydrogen carbonate (2 × 30 cm^3) and the combined aqueous extracts were acidified with dilute hydrochloric acid and extracted with ether (3 × 30 cm^3). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the *phthalate half ester* **9** as a colourless oil (11.4 g, 95%). Distillation (Kügelrohr, 180 °C/5.0 mmHg) gave colourless needles, mp 113–115 °C (Found: C, 67.2; H, 5.25. $C_{13}H_{12}O_4$ requires C, 67.2; H, 5.2%); ν_{max}/cm^{-1} 3288 (H–C≡C), 2915br (OH), 2190 (C≡C) and 1719 (C=O); δ_H(90 MHz) 1.46 (3 H, d, *J* 6.1, 1′-H), 2.05 (1 H, t, *J* 2.6, 5′-H), 2.59 (2 H, dd, *J* 6.1 and 2.6, 3′-H), 5.28 (1 H, m, 2′-H) and 7.50–7.96 (4 H, m, Ar-H); *m*/*z* (70 eV) 149 (M − C_5H_7O, 13%), 106 (100), 79 (39), 77 (21) and 28 (22); (20 eV) 106 (100%), 79 (60) and 44 (26).

Similarly prepared from (±)-pent-4-yn-2-ol and the appropriate carboxylic anhydride were: (±)-*pent-4′-yn-2′-yl hydrogen maleate* **10** (83%), a colourless oil, bp 165–170 °C/1.0 mmHg, which crystallised as colourless plates, mp 34–36 °C (Found: C, 59.1; H, 5.7. $C_9H_{10}O_4$ requires C, 59.3; H, 5.5%); ν_{max}/cm^{-1} 3293 (H–C≡C), 3100br (OH) and 1729 (C=O); λ_{max}/nm 203 (log ε 3.85); δ_H(90 MHz) 1.26 (3 H, d, *J* 6.2, 1′-H), 1.97 (1 H, t, *J* 2.7, 5′-H), 2.36 (2 H, dd, *J* 6.2 and 2.7, 3′-H), 4.99 (1 H, m, 2′-H), 6.22 (1 H, d, *J* 9.0, =CH), 6.23 (1 H, d, *J* 9.0, =CH) and 11.36 (1 H, br s, CO_2H); δ_C(22.5 MHz) 18.2 (q, C-1′), 24.8 (t, C-3′), 70.3 (d, C-2′), 70.8 (d, C-5′), 79.3 (d, C-4′), 128.7 (m, *C*HCO$_2$R), 128.8 (m, *C*HCO$_2$H), 171.3 (s, *C*O$_2$R) and 177.6 (s, CO_2H); *m*/*z* 183 (M + H, 0.5%), 99 (M − C_5H_7O, 100) and 52 (20); and (±)-*pent-4′-yn-2′-yl hydrogen succinate* **11** (87%), a colourless oil, bp 160–170 °C (Found: C, 58.6; H, 6.7. $C_9H_{12}O_4$ requires C, 58.7; H, 6.6%); ν_{max}/cm^{-1} 3289 (H–C≡C), 3200br (OH), 1728 (C=O) and 1713 (C=O); δ_H(90 MHz) 1.21 (3 H, d, *J* 6.0, 1′-H), 1.95 (1 H, t, *J* 2.7, 5′-H), 2.34 (2 H, dd, *J* 6.0 and 2.7, 3′-H), 2.53 (4 H, br s, 2-, 3-H), 4.90 (1 H, m, 2′-H) and 10.83 (1 H, br s, CO_2H); δ_C(22.5 MHz) 18.6 (q, C-1′), 25.1 (t, C-3′), 28.7 (m, *C*H$_2$CO$_2$R), 28.8 (m, *C*H$_2$CO$_2$H), 68.8 (d, C-2′), 70.4 (d, C-5′), 79.3 (d, C-4′), 171.3 (s, *C*O$_2$R) and 177.6 (s, CO_2H); *m*/*z* 101 (M − C_5H_7O, 100%), 73 (13), 66 (10) and 54 (14).

(*S*)-1-Phenylethylammonium (±)-pent-4′-yn-2′-yl phthalate

The phthalate half ester **9** (600 mg, 2.6 mmol) was dissolved in boiling acetone (4 cm^3) and (*S*)-1-phenylethylamine was added (0.29 cm^3, 1.0 equiv.). The solution was heated for a few minutes before cooling, whereupon the *title salt* was precipitated in quantitative yield. Recrystallisation gave colourless needles, mp 105–106 °C (acetone) (Found: C, 71.7; H, 6.9; N, 3.95. $C_{21}H_{23}NO_4$ requires C, 71.4; H, 6.6; N, 4.0%); ν_{max}/cm^{-1} 3287 (H–C≡C), 2931br ($^+NH_3$), 2200 (C≡C), 1719 and 1624; δ_H(400 MHz) 1.31 and 1.33 (each 3 H, d, *J* 6.4, 1′-H), 1.45 (6 H, d, *J* 6.8, 2-H), 2.000 and 2.004 (each 1 H, t, *J* 2.7, 5′-H), 2.40–2.54 (4 H, m, 3′-H), 4.19 (2 H, m, 1-H), 5.02 (2 H, m, 2′-H) and 7.19–7.63 (8 H, m, ArH); *m*/*z* 149 (M − $C_{13}H_{18}NO$, 21%), 104 (100), 76 (87), 45 (76) and 39 (28).

(±)-Pent-4′-yn-2′-yl phthalate, (−)-brucine salt

The (−)-brucine salt was obtained in quantitative yield from the phthalate ester **9** and anhydrous (−)-brucine, as colourless plates, mp 103–105 °C (acetone); ν_{max}/cm^{-1} 3428 (^+NH), 3255 (H–C≡C), 2957, 2119, 1714, 1665 and 1649; λ_{max}/nm 264 (log ε 4.10) and 300 (3.83); δ_H(400 MHz) 1.37 and 1.40 (each 2 H, t, *J* 3.2, 13-H), 1.44 and 1.45 (each 3 H, d, *J* 6.3, 5′-H), 1.65 and 1.69 (each 1 H, m), 1.98–2.04 (2 H, m, 17-H), 2.15–2.24 (2 H, dt, *J* 13.3 and 7.8), 2.48–2.56 (4 H, m, 3′-H), 2.57–2.64 (6 H, m), 2.65–2.70 (4 H, m), 3.03–3.18 (6 H, m), 3.87 and 3.90 (each 6 H, s, OMe), 3.96 (2 H, d, *J* 10.5, 20b-H), 4.06–4.25 (8 H, m), 4.33 and 4.35 (each 1 H, t, *J* 3.2, 12-H), 5.16–5.24 (2 H, m, 2′-H), 6.25 (2 H, m, NH), 6.98 (2 H, s, 1-H), 7.39 (2 H, td, *J* 7.6 and 1.1, ArH), 7.48 (2 H, td, *J* 7.6 and 1.5, ArH), 7.65 (2 H, ddd, *J* 7.1, 2.2 and 1.0, ArH), 7.74 (2 H, br d, *J* 7.8, ArH) and 7.79 (2 H, s, 4-H); *m*/*z* (70 eV) 394 [M − $C_{13}H_{12}O_4$ (brucine), 6%], 85 (65), 83 (100), 47 (20) and 18 (20); (15 eV) 395 (M − $C_{13}H_{11}O_4$, 21%), 394 (79), 149 (39), 148 (20), 104 (55) and 45 (100).

(*S*)-(+)-Propane-1,2-diol

A solution of ethyl (*S*)-lactate (33 g, 0.28 mol) in ether (150 cm^3) was added to a suspension of lithium aluminium hydride (10.2 g) in ether (200 cm^3) over 3 h. After the addition was complete the suspension was stirred for a further 3 h. Water (23.6 cm^3) was added slowly and the resulting suspension was stirred for 1.5 h. The suspension was filtered and the solid was washed thoroughly with ether (800 cm^3) and dichloromethane (800 cm^3). The solid was suspended in water (100 cm^3) and acidified to pH 1 with 1 mol dm^{-3} aqueous sulfuric acid whereupon saturated aqueous oxalic acid (100 cm^3) was added. The resulting suspension was continuously extracted with dichloromethane for 1 week. The combined ether and dichloromethane extracts and washings were combined and evaporated under reduced pressure to give the title compound (10.2 g, 48%) as a colourless liquid, bp 68–70 °C/0.1 mmHg (lit.,[11] 93 °C/18 mmHg); $[\alpha]_D^{23}$ +21.9 (*c* 0.74, H_2O) {lit.,[11] $[\alpha]_D^{20}$ +20.7 (*c* 7.5, H_2O)}; ν_{max}/cm^{-1} 3348br, 2970, 2931 and 2877; δ_H(90 MHz) 1.16 (3 H, d, *J* 6.4, 3-H), 3.3–3.7 (2 H, m, 1-H) and 3.7–3.4 (1 H, m, 2-H).

(*S*)-(−)-1-Bromopropan-2-yl acetate

To the diol described above (3.8 g, 0.05 mol) at 0 °C, was added hydrobromic acid in acetic acid (33%; 36.8 cm^3, 3.0 equiv.). Once the addition was complete (5 min) the mixture was poured into water (100 cm^3) and the mixture was neutralised with solid sodium carbonate (40 g). The product was extracted into ether (3 × 70 cm^3) and the combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was distilled to give the title compound (7.9 g, 87%) as a colourless liquid, bp 68–70 °C/18 mmHg (lit.,[11] 57 °C/11 mmHg); $[\alpha]_D^{23}$ −13.6 (*c* 0.59, $CHCl_3$) {lit., [11] $[\alpha]_D^{23}$ −13.55

(*c* 5.8, $CHCl_3$)}; ν_{max}/cm^{-1} 2984, 2934 and 1742; δ_H(90 MHz) 1.34 (3 H, d, *J* 6.4, 3-H), 2.07 (3 H, s, $COCH_3$), 3.43 (2 H, d, *J* 5.3, 1-H) and 5.11 (1 H, m, 2-H).

(*S*)-(−)-Propylene oxide 8

To a solution of the bromo acetate described above (10 g, 0.055 mol) in pentan-1-ol (20 cm^3) under nitrogen was added sodium pentoxide (1.5 mol dm^{-3}; 42 cm^3, 1.2 equiv.). Once the addition was complete, the reaction flask was placed in an oil bath at 135 °C and (*S*)-propylene oxide **8** (3.2 g, 98%) was distilled from the mixture, bp 35–36 °C (lit.,[11] 35 °C); $[\alpha]_D^{24}$ −20.2 (*c* 0.44, CCl_4) {lit.,[11] $[\alpha]_D^{22}$ −18.55 (*c* 5.04, CCl_4)}; δ_H(90 MHz) 1.31 (3 H, d, *J* 5.1, 3-H), 2.43 (1 H, dd, *J* 5.1 and 2.6, 1-H_a), 2.75 (1 H, m, 1-H_b) and 3.00 (1 H, m, 2-H).

(*S*)-(+)-Pent-4-yn-2-ol 7

To a suspension of lithium acetylide–ethylenediamine complex (7.2 g) in dimethyl sulfoxide (100 cm^3), cooled to 0 °C under nitrogen, was added (*S*)-propylene oxide (5.0 cm^3, 0.071 mol) over 10 min. After the addition was complete the mixture was allowed to warm slowly to room temperature and stirred overnight. The suspension was poured onto ice (100 cm^3) and extracted with ether (4 × 80 cm^3). The combined ether extracts were washed with brine (6 × 30 cm^3), water (2 × 30 cm^3) and dried ($MgSO_4$). Careful evaporation of the solvent under reduced pressure followed by distillation yielded (*S*)-pent-4-yn-2-ol **7** (4.1 g, 67%) as a colourless liquid, bp 126 °C; $[\alpha]_D^{26}$ +17.8 (*c* 0.22, $CHCl_3$), $[\alpha]_D^{26}$ −21.2 (*c* 0.35, ether) {lit.,[10] $[\alpha]_D^{22}$ −20.0 (*c* 26.5, ether)}; ν_{max}/cm^{-1} 3390br (OH), 3296 (≡C–H) and 2327 (C≡C); δ_H(400 MHz) 1.27 (3 H, d, *J* 6.1, 1-H), 2.07 (1 H, t, *J* 2.7, 5-H), 2.33 (1 H, ddd, *J* 16.0, 5.4 and 2.7, 3-H), 2.43 (1 H, ddd, *J* 16.0, 6.3 and 2.7, 3-H) and 4.00 (1 H, m, 2-H).

(±)-Pent-4′-yn-2′-yl (*R*)-α-trifluoromethyl-α-methoxyphenylacetate 12 and 13

(*S*)-α-Trifluoromethyl-α-methoxyphenylacetyl chloride (45 cm^3) was added to a mixture of (±)-pent-4-yn-2-ol (20 cm^3, 0.21 mmol), diisopropylethylamine (170 cm^3) and a small crystal of *N*,*N*-dimethylaminopyridine in dichloromethane (1 cm^3) under nitrogen, and the mixture was stirred at room temperature for 10 h. The reaction was quenched by the addition of 3-(dimethylamino)propylamine (3 drops) and concentrated under reduced pressure. The residue was filtered through a short column (1 × 1 cm) of silica gel (petroleum–ethyl acetate, 80:20) to give a mixture of the Mosher esters **12** and **13** as a colourless oil (59 mg, 90%); δ_H(400 MHz) 1.35 (3 H, d, *J* 6.1, 1′$_R$-H), 1.45 (3 H, d, *J* 6.4, 1′$_S$-H), 1.95 (1 H, t, *J* 2.7, 5′$_S$-H), 2.04 (1 H, t, *J* 2.7, 5′$_R$-H), 2.48 (1 H, ddd, *J* 16.9, 6.4 and 2.7, 3′$_S$-H), 2.52 (1 H, ddd, *J* 16.9, 6.1 and 2.7, 3′$_S$-H), 2.56 (1 H, dd, *J* 6.1 and 2.7, 3′$_R$-H), 3.56 (3 H, q, *J* 1.2, OMe_S), 3.59 (3 H, q, *J* 1.3, OMe_R), 5.27 (2 H, m, 2′-H) and 7.37–7.57 (10 H, m, ArH); *m*/*z* (70 eV) 189 (M − $C_6H_7O_2$, 100%); (20 eV) 189 (M − $C_6H_7O_2$, 100%).

(*S*)-Pent-4′-yn-2′-yl (*R*)-α-trifluoromethyl-α-methoxyphenylacetate 12

The *title compound* was obtained as a colourless oil in 90% yield from (*S*)-pent-4-yn-2-ol, exactly as described above [Found: (M − $C_6H_7O_2$)$^+$, 189.0530. $C_9H_8F_3O$ requires (*M* − $C_6H_7O_2$), 189.0527]; δ_H(400 MHz) 1.45 (3 H, d, *J* 6.4, 1′-H), 1.95 (1 H, t, *J* 2.7, 5′-H), 2.48 (1 H, ddd, *J* 16.9, 6.4 and 2.7, 3′-H), 2.52 (1 H, ddd, *J* 16.9, 6.1 and 2.7, 3′-H), 3.56 (3 H, q, *J* 1.2, OMe), 5.26 (1 H, m, 2′-H), 7.38–7.42 (3 H, m, ArH) and 7.54–7.55 (2 H, m, ArH); *m*/*z* (70 eV) 189 (M − $C_6H_7O_2$, 100%); (20 eV) 189 (M − $C_6H_7O_2$, 100%).

(*S*)-(−)-4-*tert*-Butyldimethylsiloxypent-1-yne 14

To (*S*)-pent-4-yn-2-ol (10 g, 0.12 mol) and imidazole (16.2 g, 2.0 equiv.) in *N*,*N*-dimethylformamide (100 cm^3) under nitrogen was added *tert*-butylchlorodimethylsilane (20 g, 1.1 equiv.) and the solution was stirred at room temperature overnight. The mixture was diluted with water (50 cm^3) and the product was extracted into ether (3 × 30 cm^3). The combined ether extracts were washed with brine (6 × 30 cm^3) and water (3 × 30 cm^3), dried ($MgSO_4$) and then concentrated under reduced pressure. The residue was distilled (Kügelrohr) to afford the *silyl ether* **14** as a colourless liquid (21.9 g, 93%), bp 70 °C/20 mmHg; $[\alpha]_D^{26}$ −0.68 (*c* 10.7) (Found: C, 66.5; H, 11.4. $C_{11}H_{22}OSi$ requires C, 66.6; H, 11.2%); ν_{max}/cm^{-1} 3312 (≡C–H) and 2122 (C≡C); δ_H(400 MHz) 0.07 (3 H, s, SiMe), 0.08 (3 H, s, SiMe), 0.89 (9 H, s, Bu^t), 1.23 (3 H, d, *J* 6.1, 5-H), 1.97 (1 H, t, *J* 2.7, 1-H), 2.24 (1 H, ddd, *J* 16.5, 7.1 and 2.7, 3-H), 2.35 (1 H, ddd, *J* 16.5, 5.5 and 2.7, 3-H) and 3.96 (1 H, ddq, *J* 7.1, 5.5 and 6.1, 4-H); δ_C(100 MHz) −4.7 (SiMe), −4.6 (SiMe), 18.1 [*C*$(CH_3)_3$], 25.2 (C-5), 25.8 [C(*C*$H_3)_3$], 29.4 (C-3), 67.6 (C-4), 69.7 (C-1) and 81.9 (C-2); *m*/*z* 159 (22%), 147 (49), 141 (M − C_4H_9, 100), 97 (67), 75 (24) and 73 (62).

Methyl (*S*)-(+)-5-*tert*-butyldimethylsiloxyhex-2-ynoate 6

To a stirred solution of the silyl ether **14** (5.0 g, 0.025 mol) in ether (90 cm^3) under nitrogen at −78 °C was added butyllithium (1.6 mol dm^{-3}; 18.9 cm^3, 1.2 equiv.). After 30 min methyl chloroformate (2.3 cm^3, 1.2 equiv.) was added and the mixture was allowed to warm slowly to room temperature. The reaction mixture was diluted with water (50 cm^3), extracted with ether (3 × 30 cm^3) and the combined ether extracts were washed with brine (3 × 30 cm^3) and water (30 cm^3), dried ($MgSO_4$) and then evaporated under reduced pressure. The residue was purified by flash chromatography (petroleum–ether, 95:5) followed by Kügelrohr distillation to give the *hexynoate* **6** as a colourless liquid (5.2 g, 82%), bp 89–90 °C/0.5 mmHg; $[\alpha]_D^{22}$ +6.5 (*c* 0.57) (Found: C, 60.7; H, 9.5. $C_{13}H_{24}O_3Si$ requires C, 60.9; H, 9.4%); ν_{max}/cm^{-1} 2243 (C≡C) and 1715 (C=O); δ_H(400 MHz) 0.07 (3 H, s, SiMe), 0.08 (3 H, s, SiMe), 0.88 (9 H, s, Bu^t), 1.24 (3 H, d, *J* 6.1, 6-H), 2.39 (1 H, dd, *J* 16.9 and 6.6, 4-H), 2.48 (1 H, dd, *J* 16.9 and 6.0, 4-H), 3.76 (3 H, s, OMe) and 4.02 (1 H, m, 5-H); δ_C(100 MHz) −4.9 (SiMe), −4.8 (SiMe), 18.0 [*C*$(CH_3)_3$], 23.5 (C-6), 25.7 [C(*C*$H_3)_3$], 29.5 (C-4), 52.5 (OMe), 66.8 (C-5), 74.1 (C-2), 87.1 (C-3) and 154.1 (C-1); *m*/*z* 199 (M − C_4H_9, 29%), 159 (43), 155 (70), 133 (53), 89 (100) and 73 (71).

Methyl (*S*)-(+)-5-*tert*-butyldimethylsiloxy-2-dimethoxymethylene-3-methylenehexanoate 5

The hexynoate **6** (3.2 g, 0.012 mol) and ketene dimethyl acetal (1.1 g, 1.0 equiv.) were heated together in a sealed tube at 165 °C for 24 h. Kügelrohr distillation yielded the *diene* **5** (1.2 g, 28%) and recovered acetylene **6** (2.2 g). The diene **5** was obtained as a pale yellow oil, bp 150 °C/0.2 mmHg; $[\alpha]_D^{22}$ +23.5 (*c* 0.38) (Found: M$^+$, 344.2020. $C_{17}H_{32}O_5Si$ requires *M*, 344.2019); ν_{max}/cm^{-1} 2952, 2855, 1712, 1649 and 1632; δ_H(400 MHz) 0.031 (3 H, s, SiMe), 0.033 (3 H, s, SiMe), 0.87 (9 H, s, Bu^t), 1.16 (3 H, d, *J* 6.1, 6-H), 2.39 (1 H, dd, *J* 16.8 and 6.6, 4-H), 2.49 (1 H, dd, *J* 16.8 and 5.9, 4-H), 3.69 (3 H, s, OMe), 3.70 (3 H, s, OMe), 3.84 (3 H, s, CO_2Me), 4.03 (1 H, m, 5-H), 4.90 (1 H, m, =CH_2) and 5.10 (1 H, m, =CH_2); *m*/*z* (70 eV) 344 (M, 0.3%), 287 (M − C_4H_9, 16), 199 (22), 159 (37), 155 (57), 133 (58), 89 (100), 75 (56), 73 (78), 59 (34), 31 (39), 29 (24) and 28 (23); (15 eV) 344 (M, 0.3%), 287 (M − C_4H_9, 16) 199 (54), 159 (55), 155 (100), 133 (78) and 75 (24).

Methyl (*S*)-(−)-3-(2′-*tert*-butyldimethylsiloxypropyl)-8-hydroxy-1,6-dimethoxy-9,10-dioxo-9,10-dihydroanthracene-2-carboxylate 16

2-Chloro-8-hydroxy-6-methoxy-1,4-naphthoquinone **15** (63 mg, 0.26 mmol) and the diene **5** (260 mg, 3.0 equiv.) were heated together in a stoppered flask at 160 °C for 4 h and then allowed

to cool slowly for 6 h. The residue was chromatographed (PLC, toluene–dichloromethane, 50:50) and the main yellow band (R_f 0.2–0.5) was isolated. Trituration with methanol gave yellow crystals that were filtered off. The mother liquors were further chromatographed (Sephadex, methanol) and the major yellow band was collected, combined with the crystalline material and the whole was recrystallised from methanol to yield the *anthraquinone* **16** (90 mg, 69%) as yellow needles, mp 118–120 °C [(±)-form, mp 102–103 °C (methanol)]; $[\alpha]_D^{22}$ −32.5 (*c* 0.46) (Found: C, 63.3; H, 6.9. $C_{27}H_{34}O_8Si$ requires C, 63.0; H, 6.7%); ν_{max}/cm^{-1} 3439, 1730, 1671, 1628 and 1585 [(±)-form, ν_{max}/cm^{-1} 3439, 1727, 1667, 1629 and 1587]; λ_{max}/nm (EtOH) 206 (log ε 3.77), 247 (3.71), 269 (3.61), 283 (3.64), 352 (3.06) and 414 (3.24); (EtOH + 1 drop 1 mol dm^{-3} aq. NaOH) 498 (log ε 3.15); δ_H(400 MHz) −0.26 (3 H, s, SiMe), −0.07 (3 H, s, SiMe), 0.78 (9 H, s, Bu^t), 1.20 (3 H, d, *J* 6.2, 3′-H), 2.76 (2 H, m, 1′-H), 3.93 (3 H, s, OMe), 3.96 (3 H, s, OMe), 3.97 (3 H, s, OMe), 4.08 (1 H, m, 2′-H), 6.73 (1 H, d, *J* 2.6, 7-H), 7.34 (1 H, d, *J* 2.6, 5-H), 8.03 (1 H, s, 4-H) and 13.14 (1 H, s, OH); δ_C(100 MHz) −5.2 (q, *J* 119, SiMe), −4.9 (q, *J* 117, SiMe), 17.9 [br s, $C(CH_3)_3$], 24.3 (q, *J* 127, C-3′), 25.7 [qp, *J* 125 and 6, $C(CH_3)_3$], 43.9 (tm, *J* 149, C-1′), 52.6 (q, *J* 148, CO_2CH_3), 56.0 (q, *J* 145, 6-OMe), 63.5 (q, *J* 146, 1-OMe), 68.6 (dq, *J* 141 and 3, C-2′), 106.9 (dd, *J* 167 and 4, C-5), 107.3 (ddd, *J* 157, 7 and 4, C-7), 111.5 (q, *J* 6), 123.4 (d, *J* 6, C-9a), 126.8 (dt, *J* 167 and 6, C-4), 134.1 (s), 134.9 (s), 137.3 (q, *J* 7), 144.9 (m, C-3), 158.3 (q, *J* 4, C-1), 165.4 (t, *J* 5), 165.8 (m), 167.1 (q, *J* 4, CO_2CH_3), 181.8 (t, *J* 5, C-10) and 186.1 (s, C-9); *m/z* 499 (M − CH_3, 1.3%), 458 (30), 457 (M − C_4H_9, 96), 429 (29), 425 (100), 351 (44), 90 (31), 73 (74) and 18 (23).

(*E*)-8-Hydroxy-1,6-dimethoxy-9,10-dioxo-3-propenyl-9,10-dihydroanthracene-2-carboxylic acid 17

To a solution of the silyl ether (±)-**16** (18 mg, 0.035 mmol) in tetrahydrofuran (0.5 cm^3) under nitrogen was added tetrabutylammonium fluoride (1 mol dm^{-3} solution in tetrahydrofuran; 70 cm^3, 2.0 equiv.). The resulting dark red solution was stirred at room temperature for 10 h and quenched by the addition of water (5 cm^3). The mixture was extracted with ethyl acetate (3 × 10 cm^3) and the combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue (PLC, toluene–ethyl formate–formic acid, 75:24:1) gave the *alkene* **17** as a yellow crystalline solid (9 mg, 68%), mp 175 °C (soft), 189–195 °C (decomp.) (toluene) (Found: M^+, 368.0896. $C_{20}H_{16}O_7$ requires *M*, 368.0896); ν_{max}/cm^{-1} 3422, 1728, 1713, 1671, 1630 and 1579; λ_{max}/nm 227 (log ε 4.08), 255sh (3.88), 294 (4.07), 420 (3.55) and 440sh (3.50); δ_H(400 MHz; [$^2H_4$]methanol) 1.96 (3 H, dd, *J* 6.6 and 1.5, 3′-H), 3.91 (3 H, s, OMe), 3.96 (3 H, s, OMe), 6.53 (1 H, dq, *J* 16.0 and 1.5, 1′-H), 6.67 (1 H, dq, *J* 16.0 and 6.6, 2′-H), 6.73 (1 H, d, *J* 2.7, 7-H), 7.22 (1 H, d, *J* 2.7, 5-H) and 8.20 (1 H, s, 4-H); *m/z* 369 (M + H, 62%), 368 (M, 76), 353 (30), 351 (34), 350 (66), 340 (34), 338 (64), 337 (100), 335 (24), 325 (28), 324 (20), 323 (49), 322 (46), 310 (32), 307 (33), 149 (26), 129 (22), 97 (24), 83 (25), 73 (33), 71 (34), 69 (34), 61 (26), 59 (40), 56 (65), 55 (20) and 54 (51).

Methyl (*S*)-(+)-8-Hydroxy-3-(2′-hydroxypropyl)-1,6-dimethoxy-9,10-dioxo-9,10-dihydroanthracene-2-carboxylate 18

To the silyl ether **16** (70 mg, 0.14 mmol) in tetrahydrofuran (2 cm^3) and 1 mol dm^{-3} aqueous sulfuric acid (1.5 cm^3) was added tetrahydrofuran (2 cm^3) until the solution became homogeneous, whereupon the mixture was stirred at room temperature overnight. The mixture was extracted with chloroform (3 × 30 cm^3) and the combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue (PLC, toluene–ethyl formate–formic acid, 50:49:1) gave two products (R_f 0.20 and 0.41) in a combined yield of 89%. The precise ratio of products varied from 30:70 to 70:30 depending on the laboratory temperature. The more polar of the two products was chromatographed (Sephadex, dichloromethane–methanol, 50:50) and recrystallised to afford the *alcohol* **18** as yellow needles (20 mg, 36%), mp 147–149 °C (chloroform–petroleum) [(±)-form, mp 140–141 °C (chloroform–petroleum)]; $[\alpha]_D^{22}$ +16.6 (*c* 0.99) (Found: C, 63.0; H, 5.05. $C_{21}H_{20}O_8$ requires C, 63.0; H, 5.0%); ν_{max}/cm^{-1} 3439, 1726, 1674, 1629 and 1583 [(±)-form, ν_{max}/cm^{-1} 3441, 2971, 1726, 1673, 1627 and 1582]; λ_{max}/nm (EtOH) 215 (log ε 4.28), 251 (4.29), 270sh (4.18), 285 (4.22) and 414 (3.77); (EtOH + 1 drop 1 mol dm^{-3} aq. NaOH) 494 (log ε 3.73); δ_H(400 MHz) 1.30 (3 H, d, *J* 6.2, 3′-H), 2.78 (1 H, dd, *J* 13.9 and 8.1, 1′-H), 2.87 (1 H, dd, *J* 13.9 and 4.4, 1′-H), 3.94 (3 H, s, OMe), 3.98 (3 H, s, OMe), 4.00 (3 H, s, OMe), 4.13 (1 H, m, 2′-H), 6.73 (1 H, d, *J* 2.6, 7-H), 7.33 (1 H, d, *J* 2.6, 5-H), 8.05 (1 H, s, 4-H) and 13.12 (1 H, s, OH); δ_C(100 MHz) 23.8 (q, *J* 125, C-3′), 43.2 (tm, *J* 126, C-1′), 52.8 (q, *J* 148, CO_2CH_3), 56.0 (q, *J* 145, 6-OMe), 63.6 (q, *J* 146, 1-OMe), 68.1 (dm, *J* 143, C-2′), 107.1 (dd, *J* 167 and 6, C-5), 107.3 (ddd, *J* 161, 7 and 5, C-7), 111.4 (q, *J* 6, C-2), 123.7 (d, *J* 6, C-9a), 125.6 (dt, *J* 167 and 5, C-4), 134.0 (s), 135.5 (s), 137.2 (m), 144.4 (m, C-3), 158.5 (q, *J* 4), 165.4 (t, *J* 4), 165.8 (m), 167.4 (m), 181.9 (t, *J* 4, C-10) and 185.9 (s, C-9); *m/z* (70 eV) 368 (M − CH_4O, 17%), 338 (30), 324 (20), 323 (25), 31 (100), 29 (59) and 16 (33); (15 eV) 368 (M − CH_4O, 79%), 339 (22), 338 (100) and 323 (25).

The less polar of the two products was further chromatographed (Sephadex dichloromethane–methanol, 50:50) to give the *lactone* **19** (27 mg, 53%) which is characterised immediately below.

(*S*)-(+)-1-*O*-Methyldermolactone {(*S*)-(+)-10-hydroxy-8,12-dimethoxy-3-methyl-3,4,6,11-tetrahydro-1*H*-anthra[2,3-*c*]pyran-1,6,11-trione} 19

A mixture of the alcohol **18** (36 mg, 0.090 mmol) and toluene-*p*-sulfonic acid (2 mg) in dichloromethane (2 cm^3) was stirred under nitrogen at room temperature for 1 h. The solvent was evaporated under reduced pressure and the residue was chromatographed (PLC, toluene–ethyl formate–formic acid, 50:49:1) to give the *lactone* **19** (33 mg, 100%) as orange coloured plates, mp 240–243 °C (ethyl acetate–petroleum) [(±)-form, yellow needles, mp 238–242 °C (ethyl acetate–petroleum)]; $[\alpha]_D^{22}$ +283.5 (*c* 0.39) (Found: C, 65.4; H, 4.3. $C_{20}H_{16}O_7$ requires C, 65.2; H, 4.4%); ν_{max}/cm^{-1} 3439, 1728, 1671, 1637 and 1584 [(±)-form, ν_{max}/cm^{-1} 3441, 1729, 1669, 1632 and 1585]; λ_{max}/nm (EtOH) 224 (log ε 3.71), 256 (3.69), 281 (3.67) and 420 (3.16); (EtOH + 1 drop 1 mol dm^{-3} aq. NaOH) 514 (log ε 2.96); δ_H(400 MHz) 1.54 (3 H, d, *J* 6.2, 3′-H), 3.05 (2 H, m, 1′-H), 3.94 (3 H, s, 6-OMe), 4.12 (3 H, s, 1-OMe), 4.62 (1 H, m, 2′-H), 6.76 (1 H, d, *J* 2.6, 7-H), 7.32 (1 H, d, *J* 2.6, 5-H), 7.96 (1 H, s, 4-H) and 13.14 (1 H, s, OH); δ_C(100 MHz) 20.6 (q, *J* 128, C-3′), 36.5 (tm, *J* 131, C-1′), 56.1 (q, *J* 145, 6-OMe), 63.7 (q, *J* 147, 1-OMe), 74.2 (dm, *J* 147, C-2′), 107.1 (dd, *J* 147 and 6, C-5), 107.7 (ddd, *J* 167, 8 and 4, C-7), 111.5 (dd, *J* 9 and 6, C-2), 121.8 (dm, *J* 167, C-4), 125.6 (m), 125.8 (m), 133.7 (s), 137.9 (s), 147.4 (m, C-3), 160.6 (s), 163.8 (m), 165.6 (t, *J* 5), 165.8 (m), 181.9 (t, *J* 5, C-10) and 185.8 (s, C-9); *m/z* 369 (M + H, 22%), 368 (M, 92), 339 (24), 338 (100), 323 (82), 310 (25) and 295 (23).

(*S*)-(+)-Dermolactone {(*S*)-(+)-10,12-dihydroxy-8-methoxy-3-methyl-3,4,6,11-tetrahydro-1*H*-anthra[2,3-*c*]pyran-1,6,11-trione} 3

To a stirred solution of the lactone **19** (16 mg, 0.043 mmol) in dichloromethane (3 cm^3) under nitrogen at 0 °C was added boron trichloride (1 mol dm^{-3} solution in dichloromethane; 0.04 cm^3, 1.0 equiv.). The resultant pink–red solution was stirred at 0 °C for 1 h and then quenched by the addition of water (1 cm^3). The resultant yellow solution was extracted with dichloromethane (3 × 15 cm^3) and the combined organic extracts were

dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography (Sephadex, methanol) gave (*S*)-(+)-*dermolactone* **3** (15.5 mg, 100%) as orange coloured needles, mp 255–257 °C (chloroform–methanol) [(±)-form, orange coloured micro-needles, mp 246–250 °C (decomp.) (chloroform–methanol)]; $[\alpha]_D^{22}$ +169.3 (*c* 0.21) (Found: C, 63.8; H, 3.7. $C_{19}H_{14}O_7$ requires C, 64.4; H, 4.0%); ν_{max}/cm^{-1} 3439, 1735, 1671, 1650 and 1604 [(±)-form, ν_{max}/cm^{-1} 3439, 1725, 1674 and 1627]; λ_{max}/nm (EtOH) 232 (log ε 3.95), 289 (3.73) and 447 (3.48); (EtOH + 1 drop 1 mol dm^{-3} aq. NaOH) 544 (log ε 3.66); δ_H(400 MHz) 1.56 (3 H, d, *J* 6.2, 3′-H), 3.04 (2 H, m, 1′-H), 3.95 (3 H, s, OMe), 4.69 (1 H, m, 2′-H), 6.73 (1 H, d, *J* 2.6, 5-H), 7.35 (1 H, d, *J* 2.6, 7-H), 7.64 (1 H, s, 4-H), 12.36 (1 H, s, 8-OH) and 13.35 (1 H, s, 1-OH); δ_C(100 MHz) 20.6 (C-3′), 36.2 (C-1′), 56.2 (6-OMe), 74.5 (C-2′), 107.3 (C-7), 108.8 (C-5), 110.2 (C-8a), 116.7 (C-9a), 117.2 (C-2), 117.3 (C-4), 134.3 (C-4a), 136.9 (C-10a), 148.7 (C-3), 164.1 (C-1), 165.7 (C-8), 166.7 (C-6 and lactone C=O), 181.4 (C-10) and 189.4 (C-9); *m/z* 354 (M, 15%), 310 (M − C_2H_4O, 30), 83 (21), 69 (28), 57 (34), 55 (42), 44 (93), 43 (48), 41 (41), 29 (21), 28 (57), 18 (100) and 17 (21).

Isolation of natural (+)-dermolactone

Fresh toadstools (140 g) of *Dermocybe sanguinea* (sensu Cleland) were finely chopped and soaked in ethanol (100 cm^3) at room temperature for 3 h. The extract was concentrated under reduced pressure and the red residue was partitioned between ethyl acetate (3 × 50 cm^3) and water (50 cm^3). The combined organic extracts were dried (Na_2SO_4) and concentrated. Chromatography of the red residue (short column, silica gel, toluene–ethyl formate–formic acid, 50:49:1) gave a red–orange fraction and a less mobile green fraction. The red fraction was further chromatographed (i, PLC, toluene–ethyl formate–formic acid, 140:60:1, 3 elutions; ii, Sephadex, methanol) to afford natural dermolactone (R_f 0.62) (2.8 mg, 2 × 10^{-2}% fr. wt.) as an orange coloured crystalline solid, mp 268–270 °C (lit.,[5] 268–271 °C); $[\alpha]_D^{22}$ +45.9 (*c* 0.21) (lit.,[5] $[\alpha]_D$ +22), that was otherwise identical with (*S*)-(+)-dermolactone **3** described above.

(±)-1-*O*-Acetyldermolactone {(±)-12-acetoxy-10-hydroxy-8-methoxy-3-methyl-3,4,6,11-tetrahydro-1*H*-anthra[2,3-*c*]pyran-1,6,11-trione} 20 and (±)-8-*O*-acetyldermolactone {(±)-10-acetoxy-12-hydroxy-8-methoxy-3-methyl-3,4,6,11-tetrahydro-1*H*-anthra[2,3-*c*]pyran-1,6,11-trione} 21

To a solution of (±)-dermolactone **3** and **4** (13 mg, 0.037 mmol) in acetic anhydride (1 cm^3) was added pyridine (1 drop) and a small crystal of *N*,*N*-dimethylaminopyridine and the stirred mixture was heated at 65 °C under nitrogen for 1.5 h. The solvent was removed under reduced pressure and the residue was chromatographed (PLC, toluene–ethyl formate–formic acid, 140:60:1, 3 elutions) to give, from the less mobile zone, (±)-8-O-*acetyldermolactone* **21** (R_f 0.20) (3 mg, 21%) as a yellow crystalline solid, mp 230–232 °C (decomp.) (dichloromethane) [Found: (M − C_2H_2O)$^+$, 354.0736. $C_{19}H_{14}O_7$ requires (M − C_2H_2O), 354.0739]; ν_{max}/cm^{-1} 3448, 2921, 1768, 1697, 1680, 1650 and 1597; λ_{max}/nm (EtOH) 203 (log ε 3.50), 231 (3.54), 279 (3.49) and 420 (2.91); (EtOH + 1 drop 1 mol dm^{-3} NaOH) 526 (log ε 2.92); δ_H(300 MHz) 1.54 (3 H, d, *J* 6.4, 3′-H), 2.46 (3 H, s, OAc), 3.01 (1 H, br d, *J* 3.5, 1′-H), 3.04 (1 H, br s, 1′-H), 3.99 (3 H, s, OMe), 4.66 (1 H, m, 2′-H), 6.94 (1 H, d, *J* 2.7, 7-H), 7.60 (1 H, s, 4-H), 7.70 (1 H, d, *J* 2.7, 5-H) and 13.96 (1 H, s, OH); δ_C(75 MHz) 20.6 (C-3′), 21.1 (CO*C*H_3), 36.4 (C-1′), 56.4 (OMe), 74.2 (C-2′), 110.4 (C-7), 116.5, 116.7, 116.8, 116.9, 117.8, 135.8, 136.2, 148.6 (C-3), 153.0 (C-8), 164.4 (C-1), 165.1, 169.3, 169.4, 181.6 (C-10) and 185.6 (C-9); *m/z* 354 (M − C_2H_2O, 5%), 313 (21), 312 (100), 295 (27), 294 (55), 283 (43), 266 (41), 251 (42), 239 (29), 152 (26), 142 (41), 139 (29), 127 (21), 115 (23), 105 (23), 91 (43), 77 (34), 76 (24), 71 (21), 69 (22), 65 (24), 62 (30), 56 (41) and 54 (31), and from the more mobile zone, (±)-1-O-*acetyldermolactone* **20** (R_f 0.45), which was obtained as a yellow crystalline solid (3 mg, 21%), mp 225–228 °C (decomp.). (dichloromethane) (Found: M$^+$, 396.0849. $C_{21}H_{16}O_8$ requires *M*, 396.0845); ν_{max}/cm^{-1} 3430, 1776, 1738, 1671, 1632 and 1598; λ_{max}/nm (EtOH) 207 (log ε 3.25), 218sh (3.20), 236 (3.20), 257 (3.24), 280 (3.23) and 423 (2.63); (EtOH + 1 drop 1 mol dm^{-3} NaOH) 526 (log ε 2.75); δ_H(300 MHz) 1.53 (3 H, d, *J* 6.0, 3′-H), 2.51 (3 H, s, OAc), 3.08 (2 H, m, 1′-H), 3.94 (3 H, s, OMe), 4.64 (1 H, m, 2′-H), 6.74 (1 H, d, *J* 2.5, 7-H), 7.34 (1 H, d, *J* 2.5, 5-H), 8.11 (1 H, s, 4-H) and 12.87 (1 H, s, OH); *m/z* 396 (M, 10%), 355 (22), 354 (M − C_2H_2O, 100), 311 (22) and 310 (71).

(±)-1-*O*-Acetyl-8-*O*-methyldermolactone {(±)-12-acetoxy-8,10-dimethoxy-3-methyl-3,4,6,11-tetrahydro-1*H*-anthra-[2,3-*c*]pyran-1,6,11-trione} 22

A suspension of 1-*O*-acetyldermolactone **20** (2.3 mg, 0.0058 mmol), chloroform (1 cm^3), silver(I) oxide (30 mg) and methyl iodide (0.5 cm^3) was stirred in the dark at room temperature for 24 h. The mixture was filtered through a pad of Celite and the filtrate was concentrated. The residue was chromatographed (PLC, toluene–ethyl formate–formic acid, 50:49:1) to give the *title compound* **22** (1.3 mg, 55%) [Found: (M − $C_2H_2O_2$)$^+$, 352.0949. $C_{20}H_{16}O_6$ requires (M − $C_2H_2O_2$), 352.0947]; ν_{max}/cm^{-1} 3422, 1726, 1676 and 1597; λ_{max}/nm 216 (log ε 3.75), 252 (3.62), 279 (3.61), 334sh (2.89) and 402 (2.86); δ_H(400 MHz) 1.52 (3 H, m partially hidden under H_2O, 3′-H), 2.52 (3 H, s, OAc), 3.08 (2 H, m, 1′-H), 4.00 (6 H, s, OMe), 4.60 (1 H, m, 2′-H), 6.82 (1 H, d, *J* 2.6, 7-H), 7.37 (1 H, d, *J* 2.6, 5-H) and 8.02 (1 H, s, 4-H); *m/z* (70 eV) 352 (M − $C_2H_2O_2$, 0.7%), 202 (27), 125 (31), 109 (43), 97 (26), 85 (53), 83 (100), 69 (40), 57 (22), 55 (47), 47 (20), 41 (63), 39 (22), 29 (22), 28 (35), 27 (22) and 18 (85); (15 eV) 352 (M − $C_2H_2O_2$, 1.1%), 125 (31), 109 (59), 97 (28), 83 (100) and 69 (25).

(*S*)-(+)-1,8-Di-*O*-methyldermolactone {(*S*)-(+)-12-hydroxy-8,10-dimethoxy-3-methyl-3,4,6,11-tetrahydro-1*H*-anthra-[2,3-*c*]pyran-1,6,11-trione} 25

To a solution of (*S*)-(+)-dermolactone **3** (2.8 mg, 0.0079 mmol) in chloroform (1 cm^3) was added methyl iodide (1 cm^3) and freshly prepared silver(I) oxide (30 mg) and the suspension was stirred in the dark for 2 days. Further portions of methyl iodide (1 cm^3) and silver(I) oxide (30 mg) were added and the suspension was stirred for 24 h. The suspension was filtered through Celite and the residue was washed with chloroform (30 cm^3). The filtrate was evaporated under reduced pressure to give (*S*)-(+)-1,8-*di*-O-*methyldermolactone* **25** as yellow needles (1.5 mg, 50%), mp 223–225 °C (ethyl acetate–petroleum) [(±)-form, mp 233–235 °C (chloroform–methanol)]; $[\alpha]_D^{22}$ +145.0 (*c* 0.21) (Found: M$^+$, 382.1052. $C_{21}H_{18}O_7$ requires *M*, 382.1052); ν_{max}/cm^{-1} 3435, 1725, 1671 and 1597 [(±)-form, ν_{max}/cm^{-1} 3443, 1726, 1671 and 1594]; λ_{max}/nm 223 (log ε 4.44), 247sh (4.19), 278 (4.30), 339 (3.55) and 398 (3.53); δ_H(400 MHz) 1.53 (3 H, d, *J* 6.2, 3′-H), 3.02 (2 H, m, 1′-H), 3.97 (3 H, s, 6-OMe), 3.99 (3 H, s, 8-OMe), 4.13 (3 H, s, 1-OMe), 4.61 (1 H, m, 2′-H), 6.81 (1 H, d, *J* 2.2, 7-H), 7.32 (1 H, d, *J* 2.2, 5-H) and 7.83 (1 H, s, 4-H); *m/z* 382 (M, 67%), 366 (63), 353 (24), 351 (89), 338 (28), 337 (100), 324 (31), 322 (25), 308 (31), 49 (22), 44 (58), 43 (33), 28 (76), 18 (87) and 16 (25).

When the Celite pad from the filtration described above, was washed with chloroform containing 1% acetic acid (30 cm^3) and then with chloroform (30 cm^3) and the filtrates were concentrated and chromatographed (PLC, toluene–ethyl formate–formic acid, 50:49:1), (*S*)-(+)-8-O-*methyldermolactone* **26** was obtained as a yellow crystalline solid (0.45 mg, 15%), mp 220 °C (subl.), 241–250 °C (decomp.) (dichloromethane) [(±)-form, mp 245–250 °C (dichloromethane)]; $[\alpha]_D^{22}$ +48.4 (*c* 0.023) (Found: M$^+$, 368.0900. $C_{20}H_{16}O_7$ requires *M*, 368.0896);

ν_{max}/cm^{-1} 3433, 1724, 1671 and 1593 [(±)-form, ν_{max}/cm^{-1} 3441, 1729, 1692, 1671, 1625 and 1593]; λ_{max}/nm (EtOH) 236 (log ε 3.62), 285 (3.45) and 434 (3.02); (EtOH + 1 drop 1 mol dm^{-3} aq. NaOH) 523 (log ε 2.95); δ_H(300 MHz) 1.54 (3 H, d, *J* 6.4, 3'-H), 3.02 (2 H, m, 1'-H), 4.01 (3 H, s, OMe), 4.04 (3 H, s, OMe), 4.62 (1 H, m, 2'-H), 6.83 (1 H, d, *J* 2.5, 7-H), 7.45 (1 H, d, *J* 2.5, 5-H), 7.56 (1 H, s, 4-H) and 14.47 (1 H, s, OH); *m/z* 368 (M, 3%), 191 (29), 153 (25), 152 (21), 69 (52), 55 (32), 44 (56), 43 (36), 41 (51), 28 (63), 18 (100) and 17 (22).

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