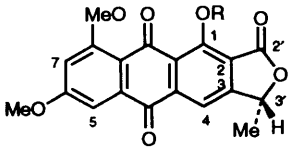
Pigments of Fungi. Part 38.[1,2] Synthesis of Austrocorticinic Acid and (*S*)-(—)-Austrocorticin; Absolute Stereochemistry of Natural Austrocorticin

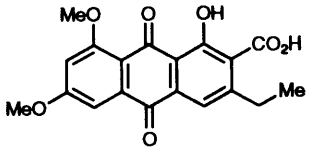
Ann S. Cotterill, Melvyn Gill,* Alberto Gimenez and Nives M. Milanovic
School of Chemistry, The University of Melbourne, Parkville, Victoria, Australia, 3052

The absolute configuration of the fungal anthraquinone (+)-austrocorticin **1** is established as (*R*) by synthesis of its antipode **5** from (*S*)-(−)-but-3-yn-2-ol *via* a Diels–Alder reaction involving the highly functionalised, chiral butadiene **6**. Similarly, austrocorticinic acid is made available from but-1-yne.

Anthraquinones bearing peripheral γ-lactone rings are extremely rare natural products. (+)-Austrocorticin **1** (no stereochemistry yet implied) was the first naturally occurring anthra[2,3-*c*]furan-1,5,10(3*H*)-trione to be isolated, and is the major pigment of the orange fruit bodies of the Australian *Dermocybe* toadstool WAT 19352.†[3,4] The quinone **1** occurs alongside several other anthraquinones, including austrocorticinic acid **4**, that are unique in that they contain a C_2 side chain at C-3 in the tricyclic nucleus.‡ It has been shown by the results of isotopic labelling experiments carried out with the intact fruit bodies that this side chain has its origins in a previously unprecedented pathway in which propionate initiates octaketide assembly.[3,4] Austrocorticin **1** is optically active



1 R = H
2 R = Ac
3 R = *p*-BrC_6H_4CO



4

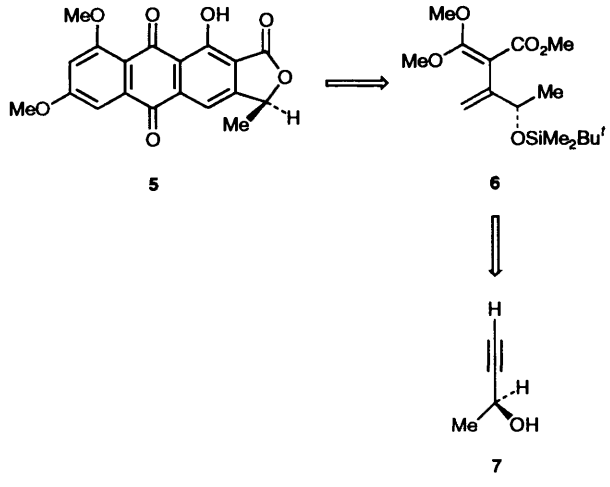
{$[\alpha]_D^{22}$ +59 (*c* 0.25 in $CHCl_3$)} but the paucity of the natural product combined with its reluctance to form nicely crystalline derivatives (*vide infra*) has precluded the determination of its absolute configuration by using degradative or X-ray crystallographic methods. Consequently, we have developed a solution to this outstanding question that involves the first total synthesis of austrocorticin in monochiral[5] form.

We have recorded elsewhere the synthesis of (±)-austrocorticin **1** + **5** *via* austrocorticinic acid **4** based on Friedel–Crafts chemistry.[6] That synthesis, unfortunately, does not lend itself readily to the synthesis of austrocorticin in optically active form. Herein we report a Diels–Alder approach to austrocorticinic acid **4** that is conveniently extended to the synthesis of (*S*)-austrocorticin **5**.

Results and Discussion

Austrocorticin **1** and its acetyl and *p*-bromobenzoyl derivatives **2** and **3**, respectively, form crystals that are unsuitable for X-ray analysis. Interestingly, the *p*-bromobenzoate **3** exists at room temperature as a mixture of atropisomers due to restricted rotation about the bond between the ester oxygen and the aromatic ring. The phenomenon is evident in the ^1H and ^{13}C NMR spectra which, at 22 °C, show doubling of the resonances corresponding to 4-H, 3′-H and the protons of the C-3′ methyl group, and to C-2, C-3 and the methyl carbon at C-3′. At 55 °C these doubled signals coalesce, only to be resolved once again as the sample is allowed to return to room temperature. The barrier to rotation (*ca.* 80 kJ mol^{-1})[7] presumably reflects the buttressing effect exerted on the bulky benzoate group by the flanking quinonoid and lactone carbonyl groups. The existence of atropisomers may go some way to explaining the difficulties encountered in obtaining the ester **3** in a highly crystalline state.

We envisaged (Scheme 1) that the tetracyclic nucleus of **5**



5 **6** **7**

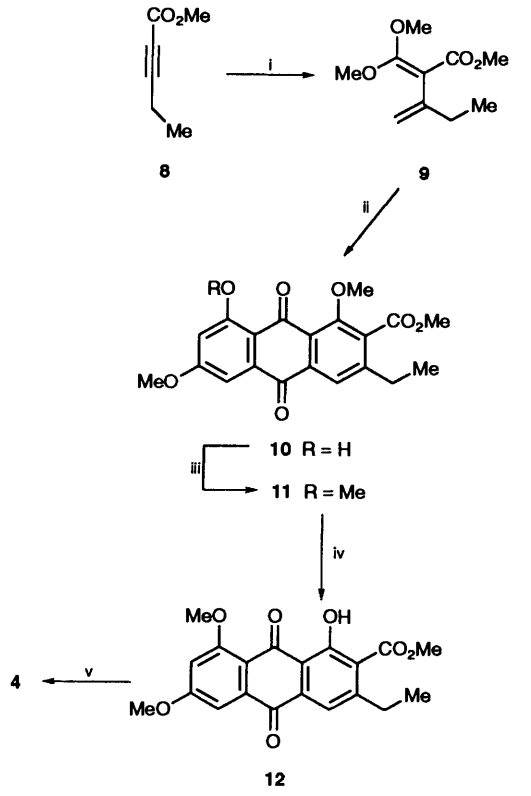
Scheme 1

should, ultimately, become available by cycloaddition between an appropriate naphthoquinone dienophile and the new chiral diene **6**. In turn, **6** appeared accessible[8] from the known (*S*)-but-3-yn-2-ol **7**.[9–11] However, before embarking on the synthesis of the chiral diene **6** we deemed it prudent to first explore the feasibility of the overall strategy as it is outlined in Scheme 1 when applied to the synthesis of the simpler natural product austrocorticinic acid **4**.

Accordingly, methyl pentynoate **8** was prepared straightforwardly in 97% yield from but-1-yne by lithiation and treatment of the resulting acetylide anion with methyl chloroformate. The five steps between **8** and austrocorticinic acid **4** are summarised in Scheme 2. Thus, cycloaddition between the pentynoate ester **8** and dimethyl ketene acetal at 160 °C in a sealed tube afforded the new diene **9** in a quantitative yield based on the amount of

† This taxon has not yet been named. The code refers to the accession number under which voucher specimens are held in the herbarium of the Royal Botanic Garden, Edinburgh.

‡ For consistency and comparison between spectroscopic data we have numbered the anthraquinone nucleus as shown in the formula for quinone **1**. The correct IUPAC name for all quinones is given in the Experimental section.



Scheme 2 *Reagents:* i, $H_2C{=}C(OMe)_2$; ii, **13**; iii, Me_2SO_4, K_2CO_3, acetone; iv, BCl_3 (1 equiv.), CH_2Cl_2; v, LiOH, DMF

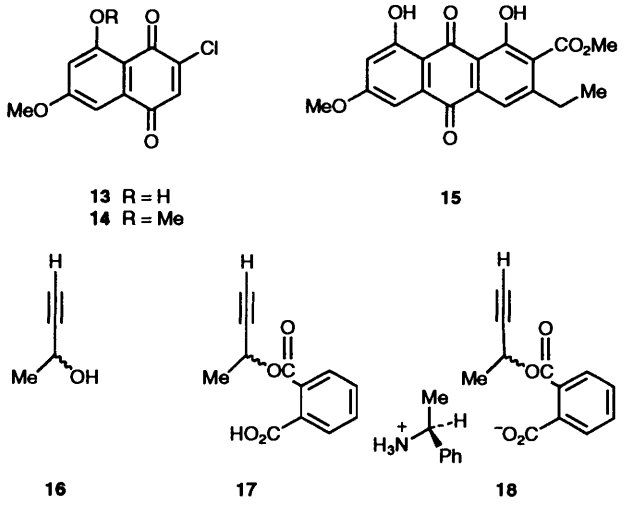
ester consumed. The ^1H NMR spectrum of **9** shows olefinic proton signals at δ 4.85 and 5.06, with singlets at δ 3.69, 3.70 and 3.86 arising from the protons of the methyl ether and methyl ester groups. The protons of the ethyl side chain give rise to characteristic resonances at δ 1.03 (t) and 2.18 (q) with J 7.3 Hz.

The chloronaphthoquinone **13**, prepared by Brassard's method from 1,3-dimethoxy-1-trimethylsilyloxybuta-1,3-diene and 2,6-dichlorobenzoquinone,[12] reacted smoothly in benzene at reflux with the diene **9**. A Diels–Alder cycloadduct was not isolated but conveniently suffered loss of hydrogen chloride and oxidation, presumably during work-up and chromatography, to afford the new anthraquinone **10**, in 80% yield. The structure **10** is in full accord with the spectroscopic data. Thus, in the ^1H NMR spectrum singlets at δ 13.15, 3.98, 3.97 and 3.93 may be assigned, respectively, to the chelated *peri* hydroxyl and the protons of the three methoxy groups. The aromatic protons appear as a singlet at δ 8.02 (4-H) and a pair of *meta* coupled doublets (J 2.6 Hz) at δ 6.72 (7-H) and 7.33 (5-H). A characteristic couplet (J 7.7 Hz) at δ 1.30 (t) and 2.71 (q) confirmed the presence in **10** of the unique ethyl side chain. Importantly, in the fully proton-coupled ^{13}C NMR spectrum of **10**, the C-10 quinonoid carbon resonates at δ 182.0 as a triplet (J 4 Hz), due to three-bond coupling with the *peri* protons 4-H and 5-H, while the signal due to C-9 appears as a sharp singlet. These data are consistent only with the substitution pattern represented by formula **10** and prove that the cycloaddition between **9** and **13** has taken place in the desired regiochemical sense. No other anthraquinone could be detected in the reaction mixture.

Methylation of the anthraquinone **10** with dimethyl sulfate and potassium carbonate in acetone at reflux gave the permethylated quinone **11** in 95% yield. A more direct route to **11** involving cycloaddition between 2-chloro-6,8-dimethoxynaphthoquinone **14** and the diene **9** required forcing conditions (160 °C, sealed tube) and afforded the permethylated quinone **11** in only 20% yield.

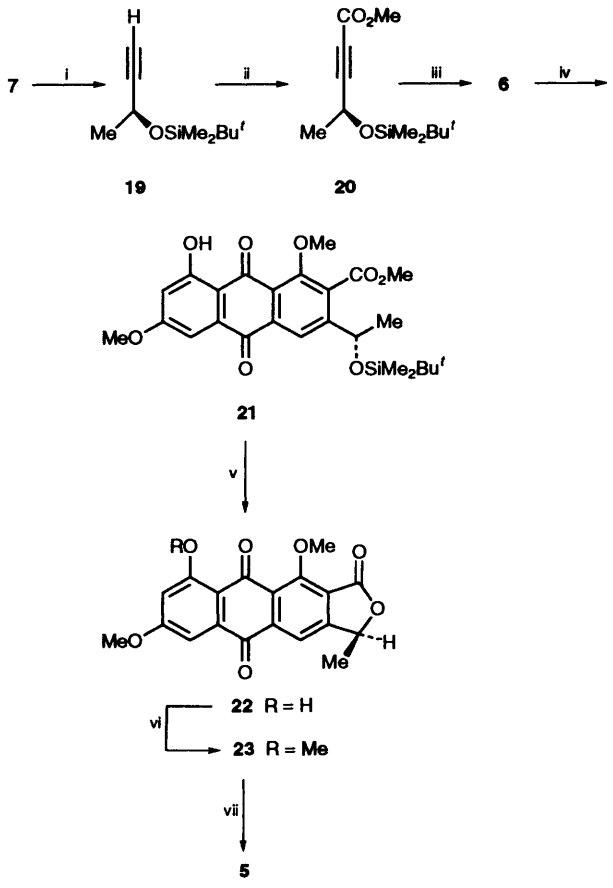
Selective cleavage of the sterically encumbered 1-*O*-methyl ether group in **11** was achieved by using 1 equiv. of boron trichloride in dichloromethane at −80 °C.[13] The product so obtained (79% yield) was freed from a modest amount (17%) of unchanged **11** by chromatography and, thereafter, proved indistinguishable from methyl austrocorticinate **12** prepared previously by the Friedel–Crafts route.[6] Attempts to achieve a higher turnover of **11** to **12** by using a larger excess of boron trichloride at higher temperature served only to diminish the isolated yield of **12**. For example, when 6 equiv. of boron trichloride were used at 0 °C, an 88% yield of the new anthraquinone **15** (δ_{OH} 12.16 and 12.47) was obtained in which both *peri* methyl ethers in **11** had been cleaved.

Finally, methyl austrocorticinate **12** was hydrolysed by using lithium hydroxide in *N*,*N*-dimethylformamide at 85 °C to give austrocorticinic acid **4**, identical in all respects with the natural product.[4]



Extension of the chemistry discussed above to the synthesis of austrocorticin in monochiral form requires a chiral diene such as **6**, or its enantiomer, of known absolute stereochemistry. To prepare such a diene we began from commercially available (±)-but-3-yn-2-ol **16**, which was resolved *via* the diastereoisomeric (*S*)-phenylethylammonium salts **18** of the phthalate half ester **17**.[9] Thus, treatment of the isochiral[5] alcohol **16** with phthalic anhydride in the presence of diisopropylethylamine at room temperature gave the half ester **17** in quantitative yield. Exposure of the ester **17** to (*S*)-phenylethylamine in acetone at reflux afforded, on cooling, colourless crystals comprising a 6:1 mixture, as monitored by ^1H NMR spectroscopy, of the diastereoisomeric salts **18**. Two recrystallisations from acetone gave a single salt, m.p. 134–136 °C, $[\alpha]_D^{22}$ −42.3 ($CHCl_3$), which, after neutralisation with 0.7 mol dm^{-3} hydrochloric acid and hydrolysis of the resulting half ester with aqueous sodium hydroxide, gave (*S*)-but-3-yn-2-ol **7**, $[\alpha]_D^{22}$ −46.4 (dioxane). The assignment of *S* chirality to **7** was initially based on comparison of the chiroptical properties of **7** with those in the literature.[9–11] However, in order to confirm the absolute configuration and to quantify the enantiomeric purity of the alcohol **7**, we have carried out ^1H NMR experiments involving the (*R*)-α-trifluoromethyl-α-methoxyphenylacetate esters (Mosher esters)[14] of (±)- and (−)-but-3-yn-2-ol, **16** and **7**, respectively. These experiments established unequivocally that the stereochemistry of **7** is *S* and that the butynol was free from its antipode at the level of detection employed (≥98% e.e.).

The seven steps between **7** and (*S*)-austrocorticin **5** are



Scheme 3 *Reagents:* i, Bu^tMe_2SiCl, imidazole, DMF; ii, BuLi, $ClCO_2Me$; iii, $H_2C{=}C(OMe)_2$; iv, **13**; v, H_2SO_4, H_2O, THF; vi, Me_2SO_4, K_2CO_3; vii, BCl_3 (1 equiv.), CH_2Cl_2

summarised in Scheme 3.* Thus, silylation of **7** gave the new silyl ether **19** as an oil in 94% yield after distillation. Metallation of **19** and exposure of the corresponding acetylide anion to methyl chloroformate yielded (81%) the novel ester **20**. A mixture of the ester **20** and dimethyl ketene acetal when heated in a sealed tube at 200 °C for 24 h furnished the chiral diene **6**, albeit in a modest yield (19%). Nevertheless, the diene **6** could be conveniently separated from a considerable quantity (*ca.* 70%) of the unchanged ester **20** by distillation and, thereafter, the ester was easily retrieved and recycled. The ^1H NMR spectrum of the diene **6** shows olefinic proton signals at δ 4.86 and 5.42, methyl singlets at δ 3.63, 3.64 and 3.87, and singlets at δ 0.03 (6 H) and 0.88 (9 H), which confirmed that the silyl ether had been retained.

Diels–Alder reaction between the diene **6** and 2-chloro-8-hydroxy-6-methoxy-1,4-naphthoquinone **13** required more forcing conditions than those employed to effect the corresponding cycloaddition involving the achiral diene **9**. Thus, it was necessary to heat **6** and **13** together without a solvent in a sealed tube at 160 °C in order to obtain the anthraquinone **21** in 78% yield after chromatographic purification. The structure of the new quinone **21** was confirmed by the spectroscopic data. Thus, the ^1H NMR spectrum shows a chelated hydroxyl resonance at δ 13.13, aromatic proton signals at δ 8.33 (4-H), 7.34 (5-H) and 6.72 (7-H), and methoxyl singlets at δ 3.93 (3 H) and 3.97 (6 H). The side-chain protons appear as a one-proton quartet at δ 4.90 coupled (J 6.4 Hz) to a three-proton doublet at δ 1.43. In turn, the fully proton-coupled ^{13}C NMR spectrum of the quinone **21** shows a singlet at δ 186.0 and a triplet (J 4 Hz) at δ 181.9 that are readily assigned to the C-9 and C-10 quinone carbonyl carbons, respectively. The multiplicities revealed that the cycloaddition process between **6** and **10** had taken place with the desired regiochemical preference.

Cleavage of the silyl ether group in **21** and concomitant lactonisation was effected in quantitative yield by treatment of **21** with dilute aqueous sulfuric acid in tetrahydrofuran during 40 h at room temperature. In the ^1H NMR spectrum of the product **22**, $[\alpha]_D^{22}$ −58.4 ($CHCl_3$), signals due to the silyl ether and methyl ester protons are no longer observed, while the lactone methine and methyl protons appear at δ 5.60 and 1.72, as a mutually coupled (J 6.8 Hz) quartet and doublet, respectively.

The anthraquinone **22** was converted into (*S*)-austrocorticin **5** in two steps. Firstly, the phenolic hydroxyl was methylated to afford the trimethoxyquinone **23**, $[\alpha]_D^{22}$ −37.1 ($CHCl_3$), in 77% yield. In the ^1H NMR spectrum of this quinone, singlet resonances at δ 3.97 and 4.00 arise from the protons of the C-6 and C-8 methoxy groups while a third, deshielded singlet at δ 4.26 is due to the methoxyl at C-1. Finally, this C-1 methoxy group was selectively cleaved by using 1 equiv. of boron trichloride at −80 °C to afford (*S*)-austrocorticin **5**, which proved to be identical in all respects, save the sign of the specific rotation, with the natural product.[4] The specific rotation reported[4] for natural austrocorticin at the sodium D line is +59, that of the synthetic (*S*)-quinone **5** at the same temperature, wavelength, and concentration in chloroform is −60.3. Thus, it is established that austrocorticin, as it occurs in the fruit bodies of the toadstool WAT 19352, must possess *R* stereochemistry at the stereogenic centre, as depicted in the formula **1**.

Experimental

General.—Where compounds have been prepared in both isochiral and monochiral forms experimental detail is described only for the optically active series. 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 100 cm^{-3}. 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 (^1H at 90 MHz, ^{13}C at 22.5 MHz) and JEOL JNM-GX400 (^1H 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 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 of the reactions shown in Scheme 3 were also performed with isochiral materials. In cases where the melting points and IR spectra of the monochiral and isochiral compounds differ, the data for the isochiral modification is quoted in the Experimental section.

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.[15] Ether refers to diethyl ether and petroleum to the hydrocarbon fraction boiling in the range 40–60 °C. Brine refers to saturated aqueous sodium chloride.

Column chromatography was performed routinely using Machery Nagel 230–400 mesh or Merck Kieselgel 60, 400–560 mesh 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.

Austrocorticin p-*Bromobenzoate* **3** [(+)-11-p-*Bromobenzoyloxy*-7,9-*dimethoxy*-3-*methylanthra*[2,3-c]*furan*-1,5,10(3H)-*trione*].—To austrocorticin **1** (10 mg), pyridine (2 cm^3) and *N*,*N*-dimethylaminopyridine (1 mg) in chloroform (2 cm^3) was added *p*-bromobenzoyl chloride (3 × *ca.* 5 mg) during 1.5 h and the mixture was stirred at room temperature for 2 h. The reaction mixture was cooled to 0 °C, diluted with chloroform (30 cm^3) and water (20 cm^3) and stirred for a further 15 min. The organic phase was washed with cold phosphoric acid (1 mol dm^{-3}; 3 × 100 cm^3) and was evaporated to dryness. The pale yellow residue (26 mg) was chromatographed (PLC, toluene–ethyl formate–formic acid, 50:49:1) to afford the p-*bromobenzoate* **3** (14 mg, 93%) as yellow needles, m.p. 208–210 °C (chloroform–hexane) (Found: C, 57.85; H, 3.5. $C_{26}H_{18}BrO_8$ requires C, 58.0; H, 3.35%); $[\alpha]_D^{22}$ +14.5 (*c* 0.5); ν_{max}/cm^{-1} 1776, 1675 and 1660; λ_{max}/nm 215 (log ε 4.64), 249 (4.30), 275 (4.00) and 400 (3.30); δ_H(400 MHz; 22 °C) 1.73 and 1.75 (total 3 H, d, *J* 6.6, 3′-Me), 3.95 (3 H, s, 6-OMe), 4.00 (3 H, s, 8-OMe), 5.63 and 5.65 (total 1 H, q, *J* 6.6, 3′-H), 6.81 (1 H, d, *J* 2.6, 7-H), 7.40 (1 H, d, *J* 2.6, 5-H), 7.70 (2 H, d, *J* 8.4, 4″-H), 8.19 (2 H, d, *J* 8.4, 3″-H), 8.24 and 8.26 (total 1 H, s, 4-H); δ_H(400 MHz, 55 °C) 1.74 (3 H, d, *J* 6.6, 3′-Me), 3.95 (3 H, s, 6-OMe), 4.00 (3 H, s, 8-OMe), 5.64 (1 H, q, *J* 6.6, 3′-H), 6.81 (1 H, d, *J* 2.6, 7-H), 7.40 (1 H, d, *J* 2.6, 5-H), 7.70 (2 H, d, *J* 8.4, 4″-H), 8.19 (2 H, d, *J* 8.4, 3″-H) and 8.24 (1 H, s, 4-H); δ_C(100 MHz, 22 °C) 20.0 and 20.1 (3′-Me), 56.1 (6-OMe), 56.7 (8-OMe), 77.2 (C-3′), 103.1 (C-5), 105.7 (C-7), 116.9 (C-8a), 118.1 (C-4), 123.9 and 124.0 (C-2), 127.9 (C-9a), 129.0 (C-5″), 131.9 (C-2″, C-3″ and C-7″), 132.3 (C-4″ and C-6″), 136.2 (C-4a), 138.8 (C-10a), 149.3 (C-1), 155.3 and 155.4 (C-3), 162.5 (C-6), 163.8 and 163.9 (C-1′), 165.6 (C-1″), 178.9 (C-9) and 182.5 (C-10); *m*/*z* 538 and 536 (M^+, 19 and 20%, respectively), 354 (27), 353 (89), 185 (91) and 183 (100).

Methyl Pent-2-ynoate **8**.—To a stirred solution of but-1-yne (5.0 cm^3, 61 mmol) in ether (90 cm^3) under nitrogen at −80 °C was added butyllithium (1.6 mol dm^{-3}; 38 cm^3, 1.1 equiv.). After 30 min, methyl chloroformate (5.65 cm^3, 1.2 equiv.) was added to the mixture which was then allowed to warm slowly to room temperature. The resulting mixture was diluted with water (50 cm^3) and extracted with ether (2 × 30 cm^3). The combined extracts were washed with brine (3 × 30 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was filtered through a short column of silica gel (petroleum–ether, 95:5) followed by Kügelrohr distillation to give methyl pent-2-ynoate **8** (6.6 g, 97%) as a colourless liquid, b.p. 60–70 °C/12 mmHg (lit.,[16] 72 °C/10 mmHg); ν_{max}/cm^{-1} 3411 (≡CH), 2983, 2953, 2243 (C≡C) and 1711 (C=O); δ_H(90 MHz) 1.21 (3 H, t, *J* 7.4, 5-H), 2.35 (2 H, q, *J* 7.4, 4-H) and 3.76 (3 H, s, OMe); δ_C(22.5 MHz) 12.81 (C-5), 12.82 (C-4), 52.2 (OMe), 70.2 (C-2), 80.3 (C-3) and 152.6 (C-1); *m*/*z* 112 (M^+, 3%), 81 (100) and 53 (32).

Methyl 2-*Dimethoxymethylene*-3-*methylenepentanoate* **9**.—Methyl pent-2-ynoate **8** (4.23 g, 0.038 mol) and dimethyl ketene acetal (3.32 g, 1.0 equiv.) were heated together in a sealed tube at 160 °C for 22 h, after which Kügelrohr distillation of the reaction mixture yielded the *diene* **9** (4.23 g, 56%) and starting acetylene **8** (1.86 g, 44%). The diene **9** was obtained as a pale yellow liquid, b.p. 110 °C/7.0 mmHg (Found: M^+, 200.1051. $C_{10}H_{16}O_4$ requires *M*, 200.1049); δ_H(400 MHz) 1.03 (3 H, t, *J* 7.3, 5-H), 2.18 (2 H, q, *J* 7.3, 4-H), 3.69 and 3.70 (each 3 H, s, OMe), 3.86 (3 H, s, CO_2Me), 4.85 (1 H, dt, *J* 1.9 and 1.0, =CH_2) and 5.06 (1 H, q, *J* 1.9, =CH_2); *m*/*z* 200 (M^+, 36%), 185 (100), 169 (31), 153 (28), 136 (26), 127 (36), 121 (45), 105 (32), 58 (43) and 51 (23).

Methyl 3-*Ethyl*-8-*hydroxy*-1,6-*dimethoxy*-9,10-*dioxoanthracene*-2-*carboxylate* **10**.—A suspension of 2-chloro-8-hydroxy-6-methoxy-1,4-naphthoquinone **13**[12] (74 mg, 0.31 mmol) and the diene **9** (220 mg, 3 equiv.) in benzene (2 cm^3) under nitrogen was heated at reflux for 4 h. After removal of the benzene under reduced pressure from the mixture the residue was chromatographed (PLC, dichloromethane–toluene, 50:50) and the fraction containing the main yellow band (R_F 0.2–0.5) was collected and evaporated. Trituration of the residue with methanol gave orange crystals. The mother liquors were chromatographed (Sephadex, methanol) and again the fraction containing the major yellow band was collected, combined with the crystalline precipitate and recrystallised to yield the *anthraquinone* **10** (92 mg, 80%) as orange coloured needles, m.p. 131–133 °C (methanol) (Found: C, 64.6; H, 4.8. $C_{20}H_{18}O_7$ requires C, 64.9; H, 4.9%); ν_{max}/cm^{-1} 3446, 2953, 1734, 1674, 1620 and 1585; λ_{max}(EtOH)/ nm 250 (log ε 4.27), 286 (4.19), 350 (2.82) and 415 (3.71); (EtOH + 1 drop 1 mol dm^{-3} aq. NaOH) 450 (log ε 3.64); δ_H(400 MHz) 1.30 (3 H, t, *J* 7.7, 2′-H), 2.71 (2 H, q, *J* 7.7, 1′-H), 3.93 (3 H, s, 6-OMe), 3.97 (3 H, s, CO_2Me), 3.98 (3 H, s, 1-OMe), 6.72 (1 H, d, *J* 2.6, 7-H), 7.33 (1 H, d, *J* 2.6, 5-H), 8.02 (1 H, s, 4-H) and 13.15 (1 H, s, OH); δ_C(100 MHz)* 14.6 (qt, *J* 128 and 4, C-2′), 26.9 (tq, *J* 128 and 4, C-1′), 52.6 (q, *J* 148, CO_2CH_3), 55.9 (q, *J* 145, 6-OMe), 63.5 (q, *J* 147, 1-OMe), 107.0 (dd, *J* 162 and 5, C-5), 108.0 (ddd, *J* 162, 6 and 4, C-7), 111.3 (q, *J* 6, C-8a), 123.2 (d, *J* 6, C-9a), 124.7 (dt, *J* 166 and 5, C-4), 134.1 (s), 135.7 (s), 136.5 (m, C-2), 149.1 (q, *J* 6, C-3), 158.1 (q, *J* 3, C-1), 165.3 (t, *J* 5.2, C-8), 165.7 (m, C-6), 167.0 (q, *J* 4, CO_2CH_3), 182.0 (t, *J* 4, C-10) and 186.0 (s, C-9); *m*/*z* 370 (M^+, 50%), 339 (31), 338 (61), 326 (21), 325 (100) and 310 (35).

Methyl 3-*Ethyl*-1,6,8-*trimethoxy*-9,10-*dioxoanthracene*-2-*carboxylate* **11**.—A mixture of the hydroxyanthraquinone **10** (77 mg, 0.21 mmol), potassium carbonate (50 mg) and dimethyl sulfate (90 mm^3,† 2 equiv.) in acetone (5 cm^3) was heated at reflux under nitrogen for 4 h. Once cool, the suspension was filtered and the filtrate concentrated. The residue was chromatographed (PLC, toluene–ethyl acetate, 50:50) to afford, after recrystallisation, the *trimethyl ether* **11** (76 mg, 95%) as fine yellow needles, m.p. 162–163 °C (chloroform–methanol) (Found: C, 65.7; H, 5.3. $C_{21}H_{20}O_7$ requires C, 65.6; H, 5.2%);

* Assignments based on {^{1}H–^{13}C}-COSY experiment.
† 1 mm^3 = 1 μl.

ν_{max}/cm^{-1} 3436, 2951, 1729, 1666 and 1594; λ_{max}/nm 282 (log ε 4.52), 345 (3.78) and 396 (3.86); δ_H(400 MHz) 1.28 (3 H, t, *J* 7.6, 2'-H), 2.67 (2 H, q, *J* 7.6, 1'-H), 3.95, 3.96, 3.97 and 3.98 (each 3 H, s, OMe), 6.78 (1 H, d, *J* 2.4, 7-H), 7.34 (1 H, d, *J* 2.4, 5-H) and 7.90 (1 H, s, 4-H); δ_C(100 MHz) 14.7 (C-2'), 26.7 (C-1'), 52.5 (CO_2CH_3), 55.9 (6-OMe), 56.6 (8-OMe), 63.6 (1-OMe), 102.3 (C-5), 105.3 (C-7), 117.8, 122.7 (C-4), 125.5, 134.8, 136.3, 136.4, 147.2 (C-3), 157.4, 162.0, 164.1, 167.5 (CO_2CH_3), 180.5 (C-10) and 183.4 (C-9); *m/z* 384 (M^+, 100%), 353 (25), 352 (45), 340 (21), 339 (100) and 324 (26).

Methyl Austrocorticinate **12** [*Methyl 3-Ethyl-1-hydroxy-6,8-dimethoxy-9,10-dioxoanthracene-2-carboxylate*].—To a stirred solution of the trimethyl ether **11** (31 mg, 0.079 mmol) in dichloromethane (1 cm^3) under nitrogen at −80 °C was added boron trichloride (1 mol dm^{-3} solution in dichloromethane; 0.08 cm^3, 1 equiv.). The resultant deep pink solution was stirred for 8 min and then quenched by the addition to it of cold, wet tetrahydrofuran (5 cm^3); it was then quickly warmed to room temperature. The resultant orange coloured solution was immediately extracted with chloroform (3 × 25 cm^3) and the combined organic extracts were dried (Na_2SO_4) and concentrated. Chromatography (PLC, toluene–ethyl formate–formic acid, 50:49:1) afforded methyl austrocorticinate **12** (R_F 0.59) (23 mg, 79%) together with recovered starting material **11** (R_F 0.34) (5.2 mg, 17%). Recrystallisation of methyl austrocorticinate **12** gave orange coloured needles, m.p. 189–190 °C (ethyl acetate–petroleum) (lit.,[6] 189–190 °C) (Found: C, 65.0; H, 5.1. Calc. for $C_{20}H_{18}O_7$: C, 64.9; H, 4.9%); ν_{max}/cm^{-1} 3440, 1722, 1665, 1624 and 1593; λ_{max}(EtOH)/nm 269sh (log ε 4.28), 283 (4.36), 423 (3.89) and 445sh (3.83); (EtOH + 1 drop 1 mol dm^{-3} aq. NaOH) 512 (log ε 3.75); δ_H(400 MHz) 1.28 (3 H, t, *J* 7.6, 2'-H), 2.69 (2 H, q, *J* 7.6, 1'-H), 3.98, 3.99 and 4.02 (each 3 H, s, OMe), 6.78 (1 H, d, *J* 2.6, 7-H), 7.45 (1 H, d, *J* 2.6, 5-H), 7.63 (1 H, s, 4-H) and 13.43 (1 H, s, OH); δ_C(100 MHz) 14.8 (qt, *J* 128 and 5, C-2'), 27.3 (tm, *J* 129, C-1'), 52.6 (q, *J* 148, CO_2CH_3), 56.1 (q, *J* 145, 6-OMe), 56.7 (q, *J* 145, 8-OMe), 104.2 (dd, *J* 165 and 4, C-5), 104.8 (dd, *J* 161 and 4, C-7), 114.9 (m), 115.0 (m), 118.6 (dt, *J* 166 and 6, C-4), 128.9 (m, C-2), 132.7 (s, C-4a), 137.4 (s, C-10a), 149.6 (m, C-3), 159.7 (d, *J* 4, C-1), 163.1 (m, C-8), 165.5 (m, C-6), 167.1 (m, CO_2CH_3), 182.4 (t, *J* 4, C-10) and 187.0 (s, C-9); *m/z* 370 (M^+, 35%), 352 (21), 339 (86), 311 (23) and 310 (100).

Methyl 3-Ethyl-1,8-dihydroxy-6-methoxy-9,10-dioxoanthracene-2-carboxylate **15**.—To a stirred solution of the trimethoxyanthraquinone **11** (65 mg, 0.17 mmol) in dichloromethane (2 cm^3) under nitrogen at 0 °C was added boron trichloride (1 mol dm^{-3} solution in dichloromethane; 0.03 cm^3, 6 equiv.) and the resultant pink solution was stirred for 1 h. The reaction was quenched by the addition to the mixture of water (5 cm^3) and the resulting orange coloured solution was extracted with dichloromethane (3 × 20 cm^3). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography (PLC, toluene–ethyl formate–formic acid, 50:49:1) of the residue gave the *anthraquinone* **15** (53 mg, 88%). Recrystallisation afforded orange coloured needles, m.p. 160–161 °C (ethyl acetate–petroleum) (Found: C, 64.2; H, 4.6. $C_{19}H_{16}O_7$ requires C, 64.0; H, 4.5%); ν_{max}/cm^{-1} 3424br, 1724, 1673, 1620 and 1604; λ_{max}(EtOH)/nm 255 (log ε 4.21), 267sh (4.19), 289 (4.18), 440 (3.96), 460sh (3.91) and 530sh (3.22); (EtOH + 1 drop 1 mol dm^{-3} aq. NaOH) 525 (log ε 3.96); δ_H(400 MHz) 1.28 (3 H, t, *J* 7.7, 2'-H), 2.71 (2 H, q, *J* 7.7, 1'-H), 3.94 and 3.99 (each 3 H, s, OMe), 6.68 (1 H, d, *J* 2.6, 7-H), 7.55 (1 H, d, *J* 2.6, 5-H), 7.69 (1 H, s, 4-H), 12.16 (1 H, s, 8-OH) and 12.47 (1 H, s, 1-OH); δ_C(100 MHz) 14.7 (qt, *J* 128 and 5, C-2'), 27.4 (tp, *J* 128 and 4, C-1'), 52.7 (q, *J* 148, CO_2CH_3), 56.1 (q, *J* 145, 6-OMe), 106.8 (ddd, *J* 163, 8 and 4, C-5), 108.7 (dd, *J* 172 and 5, C-7), 110.0 (q, *J* 6), 114.0 (m), 119.9 (dt, *J* 166 and 5, C-4), 128.7 (m, C-2), 133.6 (s), 134.9 (s), 151.2 (q, *J* 5, C-3), 159.3 (d, *J* 4, C-1), 165.3 (t, *J* 4, C-6), 166.6 (d, *J* 4, C-8), 166.8 (m, CO_2CH_3), 181.3 (t, *J* 4, C-10) and 190.3 (s, C-9); *m/z* 356 (M^+, 100%), 325 (34), 324 (M − CH_4O, 100), 296 (31) and 281 (20).

Austrocorticinic Acid **4** [*3-Ethyl-1-hydroxy-6,8-dimethoxy-9,10-dioxoanthracene-2-carboxylic Acid*].—To methyl austrocorticinate **12** (31 mg, 0.084 mmol) in *N,N*-dimethylformamide (2 cm^3) was added an excess of lithium hydroxide (37 mg) and the resulting red solution was stirred at 85 °C under nitrogen for 10 h. The mixture was acidified to pH 1 with dilute aqueous hydrochloric acid and extracted with ethyl acetate (3 × 10 cm^3). The combined extracts were extracted with aqueous sodium hydrogen carbonate (3 × 10 cm^3), after which the combined alkaline phases were acidified (pH 1) with dilute aqueous hydrochloric acid and back-extracted with chloroform (3 × 10 cm^3). After being dried (Na_2SO_4) the chloroform and ethyl acetate extracts were separately concentrated under reduced pressure to give austrocorticinic acid **4** (11 mg, 37%) and the ester **12** (10 mg, 32%), respectively. Recrystallisation of austrocorticinic acid **4** gave yellow needles, m.p. 250 °C (subl.), 280 °C (decomp.) (ethyl acetate–petroleum) [lit.,[4] 250 °C (soft), 280 °C (decomp.)] (Found: C, 63.7; H, 4.4. Calc. for $C_{19}H_{16}O_7$: C, 64.0; H, 4.5%); ν_{max}/cm^{-1} 3439, 1715, 1665, 1624 and 1591; λ_{max}(EtOH)/nm 228 (log ε 4.51), 277 (4.47), 310sh (3.98), 429 (4.01) and 445sh (3.98); (EtOH + 1 drop 1 mol dm^{-3} aq. NaOH) 517 (log ε 3.85); δ_H(400 MHz) 1.32 (3 H, t, *J* 7.3, 2'-H), 2.98 (2 H, q, *J* 7.3, 1'-H), 4.01 (3 H, s, 8-OMe), 4.05 (3 H, s, 6-OMe), 6.82 (1 H, d, *J* 2.6, 7-H), 7.49 (1 H, d, *J* 2.6, 5-H), 7.70 (1 H, s, 4-H) and 14.63 (1 H, s, OH); *m/z* 356 (M^+, 51%), 339 (22), 338 (M − H_2O, 86), 312 (28), 311 (25), 310 (67) and 309 (31).

(±)-*But-3'-yn-2'-yl Hydrogen Phthalate* **17**.—A mixture of (±)-but-3-yn-2-ol **16** (3.2 g, 0.045 mol), freshly crushed phthalic anhydride (6.66 g, 1 equiv.) and diisopropylethylamine (7.8 cm^3, 1 equiv.) in ether (50 cm^3) was stirred overnight at room temperature. The heterogeneous mixture was extracted with saturated aqueous sodium hydrogen carbonate (3 × 30 cm^3) and the combined aqueous extracts were acidified with dilute hydrochloric acid and extracted with ether (3 × 30 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to afford the title compound **17** as a colourless oil in quantitative yield. Crystallisation from chloroform–petroleum afforded colourless needles, m.p. 90–91 °C (lit.,[11] 90 °C); δ_H(90 MHz, [$^2H_6$]acetone) 1.59 (3 H, d, *J* 6.7, 1'-H), 2.53 (1 H, d, *J* 2.2, 4'-H), 5.67 (1 H, qd, *J* 6.7 and 2.2, 2'-H) and 7.50–7.94 (4 H, m, ArH); *m/z* 218 (M^+, 0.4%), 149 (M − C_4H_5O, 89), 105 (21), 104 (100), 76 (95), 70 (26), 55 (48), 53 (24), 50 (61), 43 (23), 28 (26), 27 (28), 26 (23) and 18 (33).

(S)-*Phenylethylammonium* (S)-*But-3'-yn-2'-yl Phthalate*.—The (±)-ester **17** (6.6 g, 0.030 mol) was dissolved in hot acetone (40 cm^3) to which (*S*)-phenylethylamine (3.66 g, 1 equiv.) was added. The solution was boiled for 2 min and allowed to cool slowly. The resulting colourless needles (4.67 g) were filtered off and washed with ice-cold acetone. ^{1}H NMR (400 MHz) spectroscopy showed this first precipitate to be a 6:1 mixture of diastereoisomers **18**; ν_{max}/cm^{-1} 2977 (H–C≡C), 2928br ($^+NH_3$), 2181 (C≡C), 1723 (C=O) and 1624; δ_H(400 MHz) 1.49 (d, *J* 6.8, 1'-H), 1.51 (d, *J* 6.6, 2-H), 2.48 (d, *J* 2.2, 4'$_{S,S}$-H), 2.50 (d, *J* 2.2, 4'$_{S,R}$-H), 4.30 (m, 1-H), 5.01 (br s, $^+NH_3$), 5.42 (m, 2'-H), 7.19–7.26 (m, Ar-H) and 7.31–7.63 (m, ArH). Fractional recrystallisation of the mixture from acetone provided the title salt (3.1 g, 30%, ≥97% d.e.) as colourless needles, m.p. 134–136 °C (acetone); $[\alpha]_D^{22}$ −42.3 (*c* 0.81, $CHCl_3$), $[\alpha]_D^{22}$ −6.34 (*c* 1.09, EtOH); ν_{max}/cm^{-1} 3305 (H–C≡C), 2931br ($^+NH_3$), 2198 (C≡C), 1722 (C=O) and 1621; δ_H(400 MHz) 1.49 (3 H, d, *J* 6.8, 1'-

H), 1.51 (3 H, d, *J* 6.8, 2-H), 2.48 (1 H, d, *J* 2.2, 4'-H), 4.29 (1 H, m, 1-H), 4.80 (3 H, br s, $^{+}NH_3$), 5.45 (1 H, qd, *J* 6.8 and 2.2, 2'-H) and 7.33–7.65 (9 H, m, ArH); *m/z* (70 eV) 149 (30%), 106 (100), 104 (21) and 79 (30); (20 eV) 252 (28), 236 (21), 149 (34), 120 (32), 106 (100), 105 (22), 104 (82), 70 (23), 55 (25) and 18 (51).

(S)-(−)-*But*-3'-*yn*-2'-*yl Hydrogen Phthalate*.—5 mol dm^{-3} Hydrochloric acid (5 cm^3) was added to (*S*)-phenylethylammonium (*S*)-but-3'-yn-2'-yl phthalate (2.3 g, 0.068 mol) in water (30 cm^3) and the mixture shaken until all the salt had dissolved. The mixture was extracted with ether (4 × 25 cm^3) and the combined organic extracts were dried ($MgSO_4$) and evaporated to yield the title ester as a colourless oil (1.5 g, 100%); $[\alpha]_D^{20}$ −15.6 (*c* 2.8, $CHCl_3$); −34.1 (*c* 3.0, benzene) {lit.,[10] $[\alpha]_D^{23}$ −6.6 (*c* 10.0, $CHCl_3$); lit.,[9] $[\alpha]_D^{22}$ −8.4 (benzene)}; ν_{max}/cm^{-1} 3255 (H–C≡C), 2122 (C≡C), 1725 and 1695; δ_H(90 MHz, [$^2H_6$]acetone) 1.59 (3 H, d, *J* 6.7, 1'-H), 2.53 (1 H, d, *J* 2.2, 4'-H), 5.67 (1 H, qd, *J* 6.7 and 2.2, 2'-H) and 7.50–7.94 (4 H, m, ArH); *m/z* 218 (M^+, 0.4%), 149 (M − C_4H_5O, 89), 105 (21), 104 (100), 76 (95), 70 (26), 55 (48), 53 (24), 50 (61), 43 (23), 28 (26), 27 (28), 26 (23) and 18 (33).

(S)-(−)-*But*-3-*yn*-2-*ol* **7**.—(*S*)-(−)-But-3'-yn-2'-yl hydrogen phthalate (1.4 g, 6.4 mmol) and 10 mol dm^{-3} aqueous sodium hydroxide (1.8 cm^3) were stirred together at room temperature for 2 h after which the mixture was extracted thoroughly with ether (6 × 30 cm^3). The combined extracts were dried ($MgSO_4$) and approximately 80% of the solvent was carefully removed under reduced pressure; the residue was then gently warmed to evaporate the remaining solvent to give (*S*)-but-3-yn-2-ol **7** as a colourless oil (0.4 g, 89%); $[\alpha]_D^{22}$ −42.6 (*c* 0.45, $CHCl_3$); −46.4 (*c* 1.65, dioxane); −38.1 (*c* 0.55, EtOH) {lit.,[9] $[\alpha]_D^{24}$ −40.3 (*c* 3.2, dioxane); lit.,[10] $[\alpha]_D^{24}$ −13.6 (*c* 10.0, EtOH)}; ν_{max}/cm^{-1} 3400–3250 (OH), 3295 (≡C–H) and 2111 (C≡C); δ_H(90 MHz) 1.48 (3 H, d, *J* 6.6, 1-H), 2.45 (1 H, d, *J* 2.2, 4-H) and 4.53 (qd, *J* 6.6 and 2.2, 2-H).

(±)-*But*-3'-*yn*-2'-*yl* (R)-α-*Trifluoromethyl*-α-*methoxyphenylacetates*.—(*S*)-α-Trifluoromethyl-α-methoxyphenylacetylchloride (180 mm^3) was added to a mixture of (±)-but-3-yn-2-ol **16** (70 mm^3, 0.90 mmol), diisopropylamine (0.6 cm^3) and a small crystal of *N*,*N*-dimethylaminopyridine in dichloromethane (3 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 (300 mm^3) to the mixture which was then 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 as a colourless oil (255 mg, 88%); δ_H(400 MHz) 1.51 (3 H, d, *J* 6.8, $1'_R$-H), 1.58 (3 H, d, *J* 6.6, $1'_S$-H), 2.49 (1 H, d, *J* 2.0, $4'_S$-H), 2.54 (1 H, d, *J* 2.0, $4'_R$-H), 3.55 (3 H, q, *J* 1.2, OMe_S), 3.58 (3 H, q, *J* 1.2, OMe_R), 5.62 (2 H, m, 2'-H) and 7.30–7.66 (10 H, m, ArH); *m/z* (70 eV) 189 (M − C_5H_5O, 100%), 105 (26), 77 (20), 53 (30) and 16 (33); (20 eV) 189 (M − $C_5H_5O_2$, 100%).

(S)-*But*-3'-*yn*-2'-*yl* (R)-α-*Trifluoromethyl*-α-*methoxyphenylacetate*.—The Mosher ester was obtained as a colourless oil in 88% yield from (*S*)-but-3'-yn-2-ol **7** exactly as described above [Found: $(M - C_5H_5O_2)^+$, 189.0530. $C_9H_8F_3O$ requires *M* − $C_5H_5O_2$, 189.0527]; ν_{max}/cm^{-1} 3292 (≡C–H), 2125 (C≡C) and 1751 (C=O); δ_H(400 MHz) 1.58 (3 H, d, *J* 6.6, 1'-H), 2.49 (1 H, d, *J* 2.2, 4'-H), 3.55 (3 H, q, *J* 1.2, OMe), 7.39–7.43 (3 H, m, Ar-H) and 7.53–7.54 (2 H, m, ArH); *m/z* (70 eV) 189 (M − $C_5H_5O_2$, 100%), 105 (26), 77 (20), 53 (30) and 16 (33); (20 eV) 189 (M − $C_5H_5O_2$, 100%).

(S)-(−)-2-tert-*Butyldimethylsiloxybut*-3-*yne* **19**.—To (*S*)-but-3-yn-2-ol **7** (6.83 g, 0.098 mol) and imidazole (13.3 g, 2 equiv.) in *N*,*N*-dimethylformamide (200 cm^3) under nitrogen was added *tert*-butylchlorodimethylsilane (16.1 g, 1.1 equiv.) and the resulting solution was stirred at room temperature overnight. The solution was diluted with water (50 cm^3) and extracted with ether (3 × 50 cm^3). The combined extracts were washed with brine (5 × 30 cm^3) and water (3 × 30 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was distilled (Kügelrohr) to afford the *silyl ether* **19** as a colourless liquid (16.85 g, 94%), b.p. 40–42 °C/9 mmHg; $[\alpha]_D^{22}$ −46.0 (*c* 0.086) (Found: C, 65.0; H, 11.5. $C_{10}H_{20}OSi$ requires C, 65.15; H, 10.9%); ν_{max}/cm^{-1} 3311 (≡C–H) and 2329 (C≡C); δ_H(400 MHz) 0.09 and 0.10 (each 3 H, s, SiMe), 0.90 (9 H, s, Bu^t), 1.42 (3 H, d, *J* 6.6, 1-H), 2.37 (1 H, d, *J* 2.2, 4-H) and 4.51 (1 H, qd, *J* 6.6 and 2.2, 2-H); δ_C(100 MHz) −4.7 (SiMe), −3.6 (SiMe), 18.2 [$C(CH_3)_3$], 25.7 [$C(CH_3)_3$], 58.7 (C-2), 71.1 (C-4) and 86.4 (C-3).

(S)-(−)-*Methyl* 4-tert-*Butyldimethylsiloxypent*-2-*ynoate* **20**.—To a stirred solution of the silyl ether **19** (16.8 g, 0.091 mol) in ether (60 cm^3) under nitrogen at −78 °C was added butyllithium (1.6 mol dm^{-3}; 65 cm^3, 1.2 equiv.). After 30 min methyl chloroformate (8.0 cm^3, 1.2 equiv.) was added to the mixture which was then allowed to warm slowly to room temperature. The resulting mixture was diluted with water (50 cm^3) and extracted with ether (3 × 30 cm^3). The combined extracts were washed with brine (3 × 30 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum–ether, 95:5) followed by Kügelrohr distillation to give the *ester* **20** as a colourless liquid (17.8 g, 81%), b.p. 83–84 °C/0.35 mmHg; $[\alpha]_D^{20}$ −43.1 (*c* 0.60) (Found: C, 59.3; H, 9.4. $C_{12}H_{22}O_3Si$ requires C, 59.5; H, 9.15%); ν_{max}/cm^{-1} 2237 (C≡C) and 1719 (C=O); δ_H(400 MHz) 0.12 and 0.14 (each 3 H, s, SiMe), 0.90 (9 H, s, Bu^t), 1.46 (3 H, d, *J* 6.6, 5-H), 3.77 (3 H, s, OMe) and 4.62 (1 H, q, *J* 6.6, 4-H); δ_C(100 MHz) −5.1 (q, *J* 119, SiMe), −4.7 (q, *J* 119, SiMe), 18.1 [m, $C(CH_3)_3$], 24.4 (qm, *J* 129, C-5), 25.7 [qq, *J* 125 and 5.9, $C(CH_3)_3$], 52.7 (q, *J* 148, OMe), 58.7 (dq, *J* 147 and 4, C-4), 74.9 (d, *J* 4, C-2), 89.6 (t, *J* 6, C-3) and 154.0 (s, C-1); *m/z* 199 (21%), 159 (43), 155 (72), 133 (66), 89 (100) and 73 (74).

(S)-(+)-*Methyl* 4-tert-*Butyldimethylsiloxy*-2-*dimethoxymethylene*-3-*methylenepentanoate* **6**.—The ester **20** (4.0 g, 0.017 mol) and dimethyl ketene acetal (1.5 g, 1 equiv.) were heated together in a sealed tube at 200 °C for 24 h. Kügelrohr distillation yielded the *butadiene* **6** (1.2 g, 19%) and starting acetylene **20** (2.7 g, 68%). The diene **6** was obtained as a pale yellow oil, b.p. 150–160 °C/0.2 mmHg; $[\alpha]_D^{22}$ +64.5 (*c*. 0.53) (Found: M^+, 330.1862. $C_{16}H_{30}O_5Si$ requires *M*, 330.1862); ν_{max}/cm^{-1} 2950, 2855, 1709 and 1594; δ_H(400 MHz) 0.03 (6 H, s, SiMe), 0.88 (9 H, s, Bu^t), 1.15 (3 H, d, *J* 6.5, 5-H), 3.63 and 3.64 (each 3 H, s, OMe), 3.87 (3 H, s, CO_2Me), 4.32 (1 H, qt, *J* 6.5 and 1.7, 4-H), 4.86 (1 H, m, =CH_2) and 5.42 (1 H, t, *J* 1.7, =CH_2); δ_C(100 MHz) −5.2 (SiMe), −5.0 (SiMe), 18.2 [$C(CH_3)_3$], 23.4 (C-5), 25.8 [$C(CH_3)_3$], 51.0 (CO_2CH_3), 55.7 (OMe), 69.8 (C-4), 94.0 (C-2), 113.4 (=CH_2), 146.6 (C-3), 166.6 and 167.3; *m/z* 273 (M − C_4H_9, 86%), 241 (23), 153 (45), 121 (43), 105 (21), 89 (100), 75 (34), 73 (73), 59 (47), 41 (23), 28 (62) and 15 (27).

(S)-(−)-*Methyl* 3-tert-*Butyldimethylsiloxyethyl*-8-*hydroxy*-1,6-*dimethoxy*-9,10-*dioxoanthracene*-2-*carboxylate* **21**.—2-Chloro-8-hydroxy-6-methoxynaphthoquinone **13** (57 mg, 0.24 mmol) and the diene **6** (237 mg, 3 equiv.) were heated in a sealed tube at 160 °C for 4 h. Chromatography of the crude product (PLC, toluene–dichloromethane, 50:50) gave an orange–yellow oil (R_F 0.2–0.5). This oil was further chromatographed (Sephadex, dichloromethane–methanol, 50:50) to give the

anthraquinone **21** (93 mg, 78%). Recrystallisation of this afforded yellow needles, m.p. 245–250 °C (decomp.) (methanol) [(±)-**21**, m.p. 82–84 °C (methanol)];* $[\alpha]_D^{20}$ −109.4 (*c* 0.30) (Found: C, 62.2; H, 6.4. $C_{26}H_{32}O_8Si$ requires C, 62.4; H, 6.4%); ν_{max}/cm^{-1} 3435, 1713, 1680, 1649, 1642 and 1612 [(±)-**21**, ν_{max}/cm^{-1} 3434, 1742, 1680, 1624 and 1588]; λ_{max}/nm (EtOH) 208 (log ε 4.35), 249 (4.30), 270sh (3.83), 285 (4.19), 351 (3.51) and 416 (3.75); (EtOH + 1 drop 1 mol dm^{-3} aq. NaOH) 503 (log ε 3.61); δ_H(400 MHz) −0.02 and 0.05 (each 3 H, s, SiMe), 0.90 (9 H, s, Bu^t), 1.43 (3 H, d, *J* 6.4, 2′-H), 3.93 (3 H, s, OMe), 3.97 (6 H, s, OMe), 4.90 (1 H, q, *J* 6.4, 1′-H), 6.72 (1 H, d, *J* 2.6, 7-H), 7.34 (1 H, d, *J* 2.6, 5-H), 8.33 (1 H, s, 4-H) and 13.13 (1 H, s, OH); δ_C(100 MHz) −5.0 (q, *J* 118, SiMe), 18.2 [m, $C(CH_3)_3$], 25.8 [qp, *J* 125 and 6, $C(CH_3)_3$], 26.4 (qd, *J* 128 and 3, C-2′), 52.5 (q, *J* 148, CO_2CH_3), 56.0 (q, *J* 145, 6-OMe), 63.6 (q, *J* 146, 1-OMe), 68.6 (dt, *J* 142 and 4, C-1′), 107.0 (dd, *J* 168 and 4, C-5), 107.3 (ddd, *J* 162, 7 and 4, C-7), 111.5 (q, *J* 7), 121.7 (dd, *J* 169 and 4), 124.0 (d, *J* 6), 133.9 (m), 134.2 (s), 135.9 (s), 151.9 (p, *J* 4, C-3), 158.1 (q, *J* 4, C-1), 165.4 (t, *J* 5), 165.8 (m), 166.6 (q, *J* 4), 181.9 (t, *J* 4, C-10) and 186.0 (s, C-9); *m/z* (70 eV) 443 (M − C_4H_9, 100%), 411 (61), 89 (42), 73 (30), 69 (42), 59 (23), 57 (34), 55 (29), 44 (40), 41 (41), 29 (22), 28 (41), 18 (85) and 17 (21); (15 eV) 443 (M − C_4H_9, 100%) and 411 (21).

(S)-(−)-9-*Hydroxy*-7,11-*dimethoxyanthra*[2,3-c]*furan*-1,5,10(3H)-*trione* **22**.—To a suspension of the silyl ether **21** (68.5 mg, 0.14 mmol) in tetrahydrofuran (3 cm^3) was added 1 mol dm^{-3} aqueous sulfuric acid (3 cm^3) followed by tetrahydrofuran, added dropwise until the mixture became homogeneous (*ca.* 1 cm^3). The solution was stirred at room temperature for 40 h and then extracted with chloroform (3 × 20 cm^3). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure and chromatography of the residue (PLC, toluene–ethyl formate–formic acid, 50:49:1) gave the *lactone* **22** (48 mg, 100%) as yellow needles, m.p. 215–215.5 °C (chloroform–methanol) [(±)-**22**, m.p. 230–231 °C (chloroform–methanol)]; $[\alpha]_D^{20}$ −58.4 (*c* 0.40) (Found: C, 64.3; H, 3.8. $C_{19}H_{14}O_7$ requires C, 64.4; H, 4.0%); ν_{max}/cm^{-1} 3450, 1764, 1669, 1632 and 1599 [(±)-**22**, ν_{max}/cm^{-1} 3493, 1722, 1671, 1624 and 1597]; λ_{max}/nm (EtOH) 220 (log ε 4.21), 254 (4.16), 276 (4.10) and 420 (3.55); (EtOH + 1 drop 1 mol dm^{-3} aq. NaOH) 511 nm (log ε 3.43); δ_H(400 MHz) 1.72 (3 H, d, *J* 6.8, 2′-H), 3.95 (3 H, s, 6-OMe), 4.25 (3 H, s, 1-OMe), 5.60 (1 H, q, *J* 6.8, 1′-H), 6.77 (1 H, d, *J* 2.6, 7-H), 7.35 (1 H, d, *J* 2.6, 5-H), 8.11 (1 H, s, 4-H) and 13.03 (1 H, s, OH); δ_C(100 MHz) 20.0 (qd, *J* 130 and 3, C-2′), 56.1 (q, *J* 146, 6-OMe), 63.9 (q, *J* 147, 1-OMe), 76.9 (dm, *J* 147, C-1′), 107.5 (dd, *J* 168 and 5, C-5), 107.7 (ddd, *J* 161, 7 and 5, C-7), 111.4 (m, C-2), 116.0 (d, *J* 169, C-4), 123.7 (d, *J* 6), 126.2 (m), 133.8 (s), 140.2 (s), 157.9 (m, C-3), 161.6 (m, C-1), 165.6 (t, *J* 4, C-6), 165.9 (m, C-8), 166.1 (s, lactone C=O), 181.9 (t, *J* 4, C-10) and 185.8 (s, C-9); *m/z* 355 (M + H, 21%), 354 (M^+, 100), 325 (22), 324 (96), 308 (22) and 296 (43).

(S)-(−)-1-O-*Methylaustrocorticin* **23** [(S)-(−)-7,9,11-*Trimethoxy*-3-*methylanthra*[2,3-c]*furan*-1,5,10(3H)-*trione*].—To the anthraquinone **22** (45 mg, 0.13 mmol) in acetone (5 cm^3) was added potassium carbonate (30 mg) and dimethyl sulfate (30 mm^3) and the resultant mixture was heated at reflux under nitrogen for 4 h. After cooling, the mixture was acidified with dilute aqueous hydrochloric acid and extracted with chloroform (3 × 20 cm^3). The combined extracts were washed with dilute aqueous ammonium carbonate (20 cm^3), dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue (PLC, toluene–ethyl formate–formic acid; 50:49:1) afforded the *trimethyl ether* **23** (36 mg, 77%) as orange coloured needles, m.p. 195–197 °C (ethyl acetate–petroleum) [(±)-**23**, m.p. 202–204 °C (ethyl acetate–petroleum)]; $[\alpha]_D^{22}$ −37.1 (*c* 0.73) (Found: C, 65.5; H, 4.3. $C_{20}H_{16}O_7$ requires C, 65.2; H, 4.4%); ν_{max}/cm^{-1} 3400, 1758, 1672, 1632 and 1592 [(±)-**23**, ν_{max}/cm^{-1} 3400, 1758, 1672, 1632 and 1592]; λ_{max}/nm 221 (log ε 4.43), 235sh (4.35), 280 (4.30), 341 (3.61) and 398 (3.63); δ_H(400 MHz) 1.70 (3 H, d, *J* 6.8, 2′-H), 3.97 and 4.00 (each 3 H, s, 6,8-OMe), 4.26 (3 H, s, 1-OMe), 5.57 (1 H, q, *J* 6.8, 1′-H), 6.81 (1 H, d, *J* 2.3, 7-H), 7.32 (1 H, d, *J* 2.3, 5-H) and 7.97 (1 H, br s, OH); δ_C(100 MHz) 20.2 (qd, *J* 130 and 3, C-2′), 56.0 (q, *J* 145, 6-OMe), 56.6 (q, *J* 146, 8-OMe), 64.0 (q, *J* 147, 1-OMe), 102.5 (dd, *J* 167 and 6, C-5), 105.6 (dd, *J* 167 and 4, C-7), 114.8 (d, *J* 170), 117.9 (t, *J* 6), 120.3 (m), 123.4 (d, *J* 7, C-4), 129.3 (d, *J* 6), 136.1 (s), 139.1 (s), 156.3 (m), 160.5 (m), 161.9 (m), 164.4 (m), 166.4 (s), 180.5 (s, C-10) and 185.8 (t, *J* 4, C-9); *m/z* 369 (M + H, 18%), 368 (M^+, 73), 353 (57), 339 (27), 338 (100), 310 (50), 309 (25) and 296 (43).

(S)-(−)-*Austrocorticin* **5** [(S)-(−)-11-*Hydroxy*-7,9-*dimethoxy*-3-*methylanthra*[2,3-c]*furan*-1,5,10(3H)-*trione*].—To the trimethyl ether **23** (26.5 mg, 0.072 mmol) in dichloromethane (2 cm^3) at −80 °C was added boron trichloride (1 mol dm^{-3} solution in dichloromethane, 0.07 cm^3, 1.0 equiv.). The resulting deep pink solution was stirred at −80 °C for 8 min and then quenched by the addition to it of cold, wet tetrahydrofuran (5 cm^3). The resulting orange coloured solution was immediately extracted with chloroform (3 × 20 cm^3) and the combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was chromatographed (PLC, toluene–ethyl formate–formic acid, 39:60:1) to give (S)-(−)-*austrocorticin* **5** (14 mg, 56%) and starting material **23** (6 mg, 23%). Recrystallisation of (*S*)-(−)-austrocorticin **5** gave orange coloured needles, m.p. 245–250 °C (chloroform–methanol) (lit.,[4] **1**, m.p. 246–250 °C) [lit.,[6] (±)-**1**, m.p. 146–149 °C (chloroform–methanol)]; $[\alpha]_D^{20}$ −60.3 (*c* 0.25) {lit.,[4] **1**, $[\alpha]_D^{22}$ +59 (*c* 0.25)} (Found: C, 64.4; H, 3.8. $C_{19}H_{14}O_7$ requires C, 64.4; H, 4.0%); ν_{max}/cm^{-1} 3439, 1768, 1680, 1632 and 1596; λ_{max}/nm (EtOH) 230 (log ε 3.59), 273 (3.39), 358 (2.98) and 430 (3.07); (EtOH + 1 drop 1 mol dm^{-3} aq. NaOH) 503 (log ε 3.20); δ_H(400 MHz) 1.69 (3 H, d, *J* 7.0, 2′-H), 4.02 (3 H, s, 6-OMe), 4.06 (3 H, s, 8-OMe), 5.55 (1 H, q, *J* 7.0, 1′-H), 7.48 (1 H, d, *J* 2.6, 5-H), 7.73 (1 H, s, 4-H) and 14.23 (1 H, s, OH); *m/z* 354 (M^+, 62%), 337 (23), 336 (M − CH_4O, 100), 308 (44) and 307 (21).

Acknowledgements

This work was generously supported by a grant from the Australian Research Council. ASC and AG are grateful recipients, respectively, of an Australian Postgraduate Research Award and a Melbourne University Postgraduate Award.

References

1 Part 37, M. Gill and M. J. Kiefel, *Aust. J. Chem.*, 1994, **47**, 1967.
2 Preliminary communication: A. S. Cotterill and M. Gill, *Tetrahedron Lett.*, 1993, **34**, 3155.
3 M. Gill and A. Giménez, *J. Chem. Soc., Chem. Commun.*, 1988, 1360.
4 M. Gill and A. Giménez, *J. Chem. Soc., Perkin Trans. 1*, 1990, 1159.
5 J. W. Cornforth, *Aust. J. Chem.*, 1993, **46**, 157.
6 A. S. Cotterill and M. Gill, *Aust. J. Chem.*, 1994, **47**, 1363.
7 D. H. Williams and I. Fleming, *Spectroscopic Methods in Organic Chemistry*, 4th edn., McGraw-Hill, London, 1989, p. 103.
8 K. C. Brannock, R. D. Burpitt and J. G. Thweatt, *J. Org. Chem.*, 1963, **28**, 1697.

* Such a difference in melting point between the monochiral and isochiral forms is consistent with the latter crystallising as a 'racemic compound', that is, where antipodes are paired at the level of the unit cell.[17] This phenomenon also leads to differences in the solid state IR spectra that are noted.

9 R. Weidmann, A. Schoofs and A. Horeau, *Bull. Soc. Chim. Fr.*, 1976, 645.
10 E. R. H. Jones, J. D. Loder and M. C. Whiting, *Proc. Chem. Soc.*, 1960, 180.
11 C. S. L. Baker, P. D. Landor, S. R. Landor and A. N. Patel, *J. Chem. Soc.*, 1965, 4348.
12 J. Banville and P. Brassard, *J. Org. Chem.*, 1976, **41**, 3018.
13 C. F. Carvalho, A. V. Russo and M. V. Sargent, *Aust. J. Chem.*, 1985, **38**, 777.
14 J. A. Dale, D. L. Dull and H. S. Moser, *J. Org. Chem.*, 1969, **34**, 2543; I. Ohtani, T. Kusumi, Y. Kashman and H. Kakisawa, *J. Am. Chem. Soc.*, 1991, **113**, 4092.
15 D. D. Perrin and W. L. F. Armarego, *Purification of Laboratory Chemicals*, 3rd edn., Pergamon, Oxford, 1988.
16 J. Buckingham (ed.), *Dictionary of Organic Compounds*, 5th edn., Chapman and Hall, New York, 1982.
17 E. L. Eliel, *Stereochemistry of Carbon Compounds*, McGraw–Hill, New York, 1962, pp. 43–47.

Paper 4/04168B
Received 8*th July* 1994
Accepted 15*th August* 1994