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Synthesis of (*S*)-(-)-Austrocorticin and (*S*)-(+)-Dermolactone: Absolute Stereochemistry of the Natural Products.[1]

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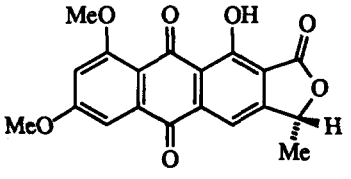
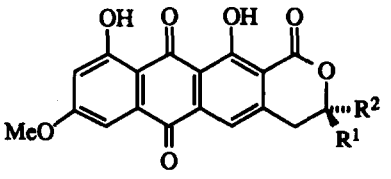
Abstract: The anthraquinones (*S*)-(-)-austrocorticin (**9**) and (*S*)-(+)-dermolactone (**2**) are synthesised using the chiral dienes **6a** and **6b**, respectively; comparison with these synthetic compounds establishes that natural austrocorticin has the (*R*) absolute configuration while dermolactone occurs naturally as a mixture of enantiomers in which the (*S*) isomer predominates.

Anthraquinones bearing peripheral γ- and δ-lactone rings are extremely rare natural products. (+)-Austrocorticin (**1**) (no stereochemistry yet implied) is the major pigment in the fruit bodies of the Australian *Dermocybe* toadstool WAT 19352.[2] It is the first naturally occurring anthra[2,3-*c*]furan-1,5,10(3*H*)-trione and, along with several other anthraquinones from the same fungus, is derived biosynthetically by way of a unique propionate initiated 'octaketide' pathway.[2] (+)-Dermolactone, (**2**) or (**3**), is the major anthraquinone in the fruit bodies of the Australian fungus *Dermocybe sanguinea* (sensu Cleland).[3] Both of the quinones **1** and **2/3** contain a chiral centre in the lactone ring but the paucity of natural materials combined with their reluctance to form nicely crystalline derivatives has so far precluded the determination of their absolute stereochemistry by degradative or X-ray crystallographic methods. We report here a solution to this outstanding question involving synthesis of both quinones in homochiral form.



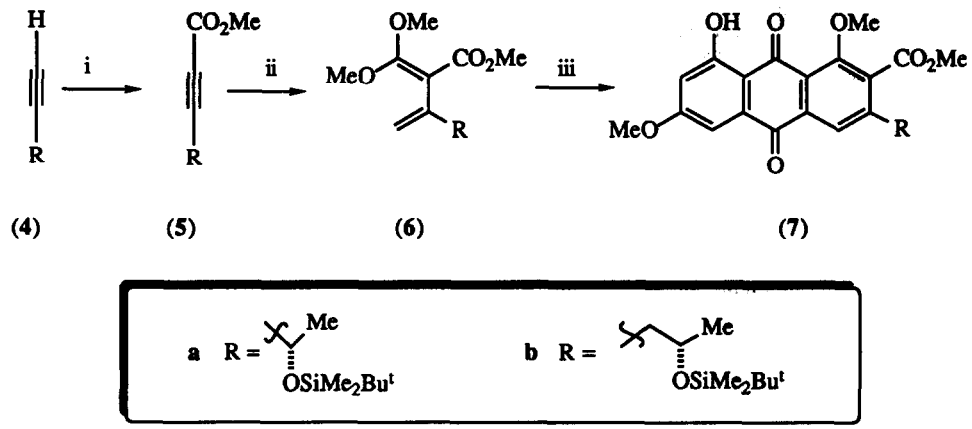
(**1**)



(**2**) $R^1 = Me$, $R^2 = H$
(**3**) $R^1 = H$, $R^2 = Me$

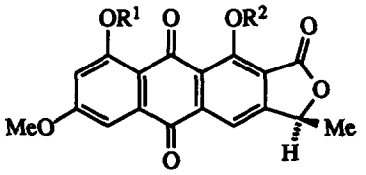
(*S*)-Austrocorticin (**9**) and (*S*)-dermolactone (**2**) were obtained along parallel lines involving incorporation of the requisite chirality and tetracyclic ring structure during regiospecific Diels-Alder reaction involving the new chiral butadienes **6a** and **6b** (Scheme 1). To our knowledge this is the first occasion on which such highly functionalised, chiral butadienes have been made and used for anthraquinone synthesis.

(*S*)-3-Butyn-2-ol, $[\alpha]_D$ -42.6°,[4] ≥ 97% e.e. by Mosher method,[5] was obtained from the racemate by classical resolution with (*S*)-phenylethylamine of the hydrogen phthalate ester,[6] and was subsequently silylated to afford **4a**, $[\alpha]_D$ -46.0°.[7] Metallation of the acetylene **4a** (Scheme 1) and treatment of the acetylide so formed with methyl chloroformate gave the ester **5a**, $[\alpha]_D$ -43.1°, which with ketene dimethyl acetal[8] afforded the new chiral diene **6a**, $[\alpha]_D$ +64.5°. Diels-Alder cycloaddition between the diene **6a** and 2-chloro-8-hydroxy-6-methoxynaphthoquinone[9] gave, after aromatisation, a single anthraquinone, m.p. 245-250°C, $[\alpha]_D$ -109.4°, that was identified unequivocally as **7a** from the spectroscopic data.[10] Acid catalysed hydrolysis and concomitant lactonisation of **7a** (H_2SO_4, THF-H_2O, r.t. 40h) led efficiently to the quinone **8**, m.p. 215°C, $[\alpha]_D$ -58.4°, which was sequentially *O*-methylated (Me_2SO_4, K_2CO_3, acetone, 56°C) and selectively demethylated (1 eq. BCl_3, $CHCl_3$, -80°C, 8 min.) to afford (*S*)-austrocorticin (**9**), m.p. 245-250°C, $[\alpha]_D$ -60.3°. The synthetic quinone was identical in all respects, save specific rotation, with the natural product. Comparison of the chiroptical data of **9** with that reported for austrocorticin from WAT 19352 {$[\alpha]_D$ +59°}[2] establishes (*R*) chirality for the fungal metabolite.

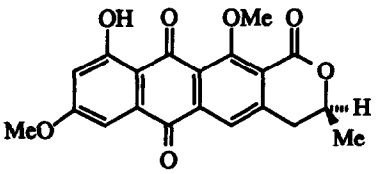


Scheme 1. Reagents: i, BuLi, $ClCO_2Me$, ether, -80°C⟶r.t.; ii, $H_2C.C(OMe)_2$, 200°C, 24h; iii, 2-chloro-8-hydroxy-6-methoxynaphthoquinone, 160°C, 4h.

(*S*)-4-Pentyn-2-ol resisted all efforts at resolution from the racemate. Consequently, it was prepared (≥97% e.e. by Mosher analysis) from (*S*)-propylene oxide and lithium acetylide.[11] Subsequent reactions (Scheme 1) served to silylate this alcohol and convert the ether **4b**, $[\alpha]_D$ -0.68°, to the ester **5b**, $[\alpha]_D$ +6.5°, and the diene **6b**, $[\alpha]_D$ +23.5°, which was allowed to react with 2-chloro-8-hydroxy-6-methoxynaphthoquinone to afford the anthraquinone **7b**, m.p. 118-120°C, $[\alpha]_D$ -32.5°. Hydrolysis of **7b** and lactonisation gave the quinone **10**, m.p. 240-243°C, $[\alpha]_D$ +283.5°, which with boron trichloride at 0°C gave (*S*)-dermolactone (**2**), m.p. 255-257°C, $[\alpha]_D$ +169.3°, identical in all respects except its optical activity with the natural product.



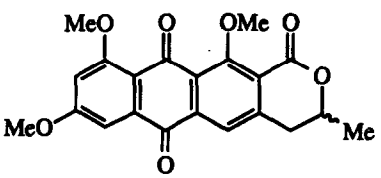
(8) $R^1 = H$, $R^2 = Me$
(9) $R^1 = Me$, $R^2 = H$



(10)

The specific rotation at the sodium D-line of dermolactone isolated from *D. sanguinea* (sensu Cleland) is +45.9°.[12] Such a large discrepancy in the magnitude of the $[\alpha]_D$ values exhibited by the natural and synthetic dextrorotatory enantiomers of dermolactone was disconcerting and, consequently, its cause was explored further by using ^{1}H-n.m.r. spectroscopy in the presence of a chiral shift reagent. Thus, racemic dermolactone [(2)+(3)] was prepared from (±)-4-pentyn-2-ol as described above in the homochiral series and was subsequently methylated (excess MeI, Ag_2O, $CHCl_3$, 3 days) to afford **11**. Addition of successive aliquots of Eu-(+)-(hfc)$_3$ to a sample of **11** in deuteriochloroform caused shifts in the signals arising from the three methoxyl groups.[13] Of particular note, the signals arising from the 1- and 6-*O*-methyl groups in **11** were each shifted and resolved into equally intense pairs of singlets with Δδ 0.017 and 0.004 p.p.m., respectively. A parallel experiment involving the 1,8-di-*O*-methyl ether of (*S*)-dermolactone (**2**) established that the component of each pair of signals that appears at higher field arises from the (*S*)-enantiomer **2**. Finally, a similar experiment with the corresponding dimethyl ether of natural dermolactone clearly revealed that the fungal metabolite is composed of a mixture of enantiomers in which the (*S*)-enantiomer **2** is in excess by 29% over its (*R*)-antipode **3**. The ratio of enantiomers thus determined by ^{1}H-n.m.r. spectroscopy is in close agreement with that calculated from the respective $[\alpha]_D$ values (27% e.e.).

The stereochemical relationship between dermolactone and the other nonaketide metabolites[3] of *Dermocybe sanguinea* (sensu Cleland) will be discussed in the full paper.



(11)

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4. Specific rotations were measured using a Perkin-Elmer MC241 polarimeter for solutions in chloroform at 20°C.
5. J. A. Dale, D. L. Dull and H. S. Mosher, *J. Org. Chem.*, 1969, **34**, 2543; I. Ohtani, T. Kusumi, Y. Kashman and H. Kakisawa, *J. Am. Chem. Soc.*, 1991, **113**, 4092.
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7. All new compounds have been fully characterised by combustion analysis and/or high resolution mass spectrometry. All spectroscopic data are in full accord with the structures proposed.
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10. Selected data for **7a**. ^{1}H-n.m.r. (400 MHz; $CDCl_3$): δ_H -0.02 (3 H, s, SiMe), 0.05 (3 H, s, SiMe), 0.90 (9 H, s, Bu^t), 1.43 (3 H, d, *J* 6.4 Hz, 2'-H), 3.93 (3 H, s, OMe), 3.97 (6 H, s, OMe), 4.90 (1 H, q, *J* 6.4 Hz, 1'-H), 6.72 (1 H, d, *J* 2.6 Hz, 7-H), 7.34 (1 H, d, *J* 2.6 Hz, 5-H), 8.33 (1 H, s, 4-H) and 13.13 (1 H, s, OH). ^{13}C-n.m.r. (100 MHz; $CDCl_3$) δ_C -5.0 (q, *J* 118 Hz, SiMe), 18.2 (m, $C(CH_3)_3$), 25.8 (qp, *J* 125 and 6 Hz, $C(CH_3)_3$), 26.4 (qd, *J* 128 and 3 Hz, C-2'), 52.5 (q, *J* 148 Hz, CO_2CH_3), 56.0 (q, *J* 145 Hz, 6-OMe), 63.6 (q, *J* 146 Hz, 1-OMe), 68.6 (dt, *J* 142 and 4 Hz, C-1'), 107.0 (dd, *J* 168 and 4 Hz, C-5), 107.3 (ddd, *J* 162, 7 and 4 Hz, C-7), 111.5 (q, *J* 7 Hz), 121.7 (dd, *J* 169 and 4 Hz), 124.0 (d, *J* 6 Hz), 133.9 (m), 134.2 (s), 135.9 (s), 151.9 (p, *J* 4 Hz, C-3), 158.1 (q, *J* 4 Hz, C-1), 165.4 (t, *J* 5 Hz), 165.8 (m), 166.6 (q, *J* 4 Hz), 181.9 (t, *J* 4 Hz, C-10) and 186.0 (s, C-9).
11. W. Francke, University of Hamburg, personal communication. We thank Professor Francke for experimental details.
12. The specific rotation of dermolactone as originally reported from *D. sanguinea* (sensu Cleland) is +22° (*c* 0.07 in $CHCl_3$).[2] We have isolated dermolactone from the same organism and rigorously purified the sample to constant rotation; in our hands dermolactone exhibits $[\alpha]_D$ +45.9° (*c* 0.21 in $CHCl_3$).
13. (±)-Dermolactone-1,8-di-*O*-methyl ether (**11**): δ_{OMe} 3.97 (6-OMe), 3.99 (8-OMe) and 4.13 (1-OMe). After addition of Eu-(+)-(hfc)$_3$ (3 mg) the signal due to 6-OMe is moved downfield by *ca.* 0.1 p.p.m. and is resolved into two singlets ($\Delta\delta$ 0.004 p.p.m.), the 8-OMe signal is moved downfield and broadened to obscurity, and the signal due to 1-OMe is moved slightly upfield and resolved into two singlets ($\Delta\delta$ 0.017 p.p.m.).

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