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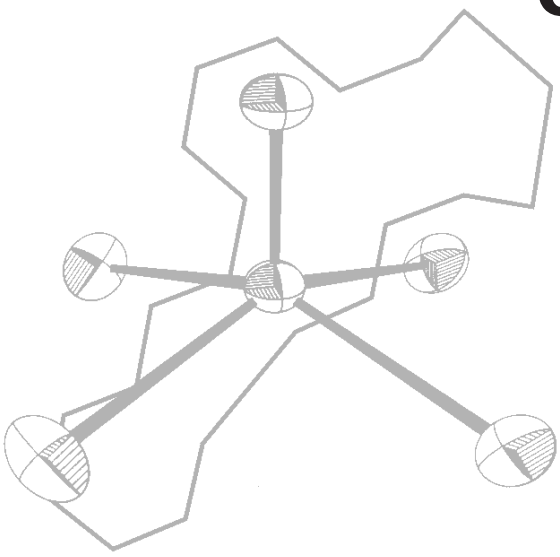

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Pigments of Fungi. LIX*†
Synthesis of (1*S*,3*S*)- and (1*R*,3*R*)-Austrocortilutein and (1*S*,3*S*)-Austrocortirubin from Citramalic Acid

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The naturally occurring tetrahydroanthraquinone (1*S*,3*S*)-austrocortilutein (1) is synthesized for the first time in enantiomerically pure form by Diels–Alder cycloaddition between the functionalized butadiene derivative (8) and the chiral 1,3-dihydroxy-1,2,3,4-tetrahydro-5,8-naphthoquinone (9), the latter being derived from (*R*)-citramalic acid (3). The natural products (1*S*,3*S*)-austrocortirubin (2) and (1*R*,3*R*)-austrocortilutein (5) were also prepared for the first time by using the same strategy.

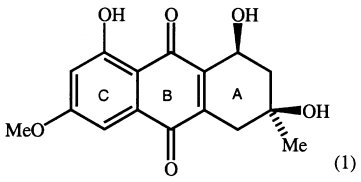
Keywords. Diels–Alder cycloaddition; functionalized butadiene; quinone.

Introduction

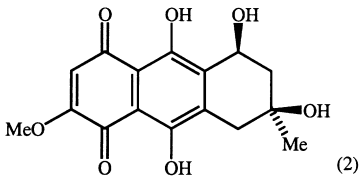
The fruiting bodies of the Australasian fungus *Dermocybe splendida* owe their spectacular colour to the presence of mixtures of yellow and red tetrahydroanthraquinone pigments that consist predominantly of (1*S*,3*S*)-austrocortilutein (1) and (1*S*,3*S*)-austrocortirubin (2).[1]‡ These were the first tetrahydroanthraquinones to be isolated from the higher fungi and they are of special significance because of their activity at low concentration against not only a range of Gram-positive and Gram-negative bacteria and fungi[1] but also against melanoma cancer cells. The structure and stereochemistry of these two compounds and their synthesis in isochiral[3] form have been described in earlier papers in this series.[1,4] We report here the first total synthesis of (1*S*,3*S*)-austrocortilutein (1) and (1*S*,3*S*)-austrocortirubin (2) in monochiral[3] form beginning from (*R*)-citramalic acid (3). (1*R*,3*R*)-Austrocortilutein (5), which we have isolated from a toadstool that is closely related to *D. splendida* (see below), is synthesized likewise beginning from (*S*)-citramalic acid (4).

Results and Discussion

Our previous synthesis of the isochiral pigments (1) and (2) involved a Diels–Alder reaction between the naphthopurpurin acetal (6) (as the precursor to the BC ring system) and isoprene as the first step of the sequence (Scheme 1).[4] Our approach to the pigments (1) and (2) in monochiral form also involves a Diels–Alder cycloaddition reaction, but in this case one that takes place late in the synthetic sequence and involves the chiral tetrahydronaphthoquinone dienophile (9) as the AB ring precursor (Scheme 2). Our reasons for not developing the earlier strategy in a monochiral sense [for example, by asymmetric dihydroxylation[5] of the olefinic double bond in the intermediate quinone (7)] include, *inter alia*, the chemical inefficiency of the later steps in that sequence.[4] Consequently, we devised the approach to (1*S*,3*S*)-austrocortilutein (1) that is represented in retrosynthetic terms in Scheme 2. Thus, we envisaged that



(1)



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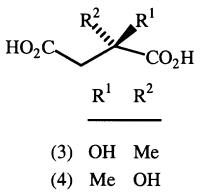
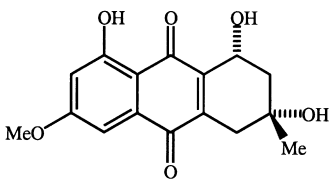


	R^1	R^2
(3)	OH	Me
(4)	Me	OH



(5)

* This paper is dedicated to Professor D. W. Cameron with thanks for his support, guidance and friendship and in recognition of his contribution, over many year, to quinone chemistry.
† Part LVIII, *Aust J. Chem*., 1999, **52**, 1035; Part LX, *Nat. Prod. Lett*., 2000, in press; Part LXI, *Aust. J. Chem*., 1999, **52**, 989.
‡ The quinones (1) and (2), and some minor quinones, are present in the intact toadstools mostly as the corresponding 8-*O*-β-D-gentiobiosides.[2]

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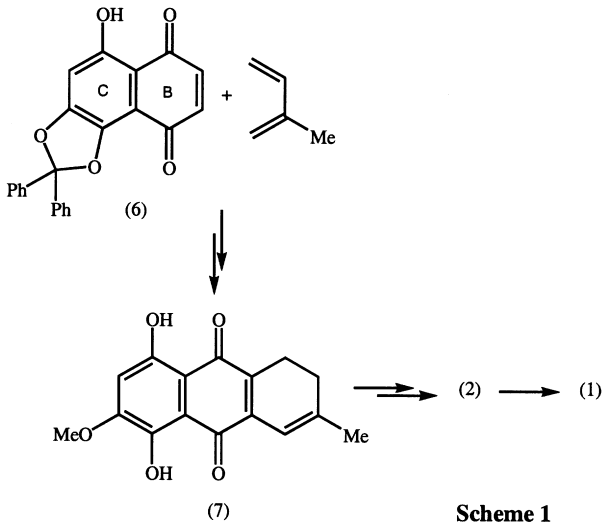
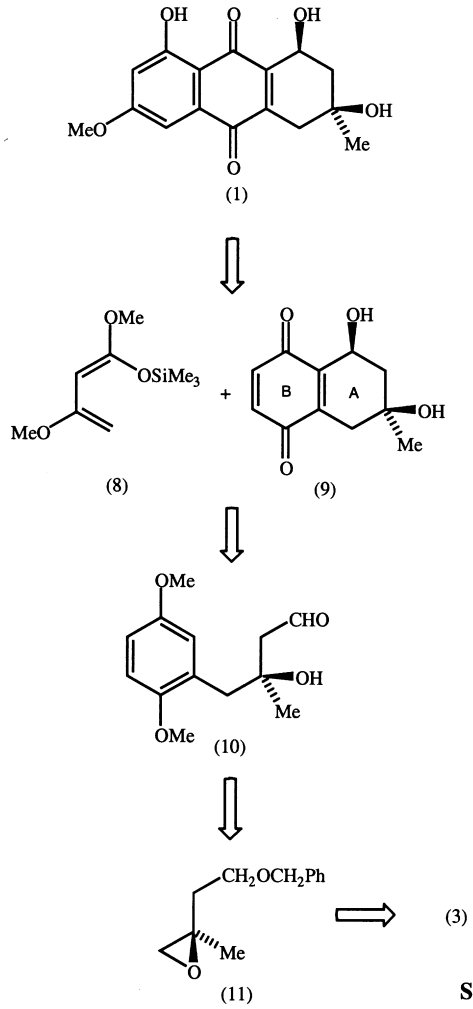
1,3-dihydroxytetrahydroanthraquinones such as (1*S*,3*S*)-austrocortilutein (1) should be accessible by way of a Diels–Alder reaction between 1,3-dimethoxy-1-trimethylsilyloxybuta-1,3-diene (8)[6] and the hitherto unknown chiral tetrahydronaphthoquinone (9). Furthermore, the quinone (9) should itself be available by an intramolecular Friedel–Crafts reaction of the chiral aldehyde (10). In turn, the aldehyde (10) would result from opening of the chiral oxiran (11) with the Grignard or cuprate reagent derived from 2-bromo-1,4-dimethoxybenzene. The chiral oxiran (11) is available, in principle, in both enantiomeric forms from citramalic acid by methods developed earlier in our laboratory for other purposes.[7]

There were several stereochemical questions that needed to be addressed before this plan could be put into practice. Firstly, the Diels–Alder reaction between (8) and (9) must be regioselective in the desired sense. In this regard it was expected that the C 1 hydroxy group* in (9) would promote the regioselectivity shown by hydrogen bonding to some degree to the *peri*-quinone carbonyl group. It is well known that hydrogen bonding of naphthoquinone carbonyl groups by *peri*-phenolic hydroxy groups is a powerful control element during cycloaddition processes.[8] Secondly, the intramolecular Friedel–Crafts reaction of the chiral aldehyde (10) *en route* to the 1,3-diol (9) must proceed with a high degree of stereoselectivity. Fortunately, it is known that the use of certain Lewis acids in such reactions is chelation-controlled and should promote the desired outcome in the present case.[9] Both of these aspects of the process will be discussed in more detail as they appear later in this paper.

The source of chirality in the retrosynthesis shown in Scheme 2 is citramalic acid, which is commercially available in both enantiomeric forms. Unfortunately, the commercial material is expensive [e.g., $37/g for the (*R*)-enantiomer (3) from Aldrich©] and, because of its position at the beginning of the sequence, we considered it preferable to pursue a more economical source of this raw material.

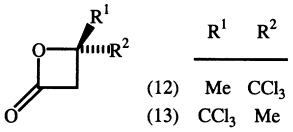


Scheme 1

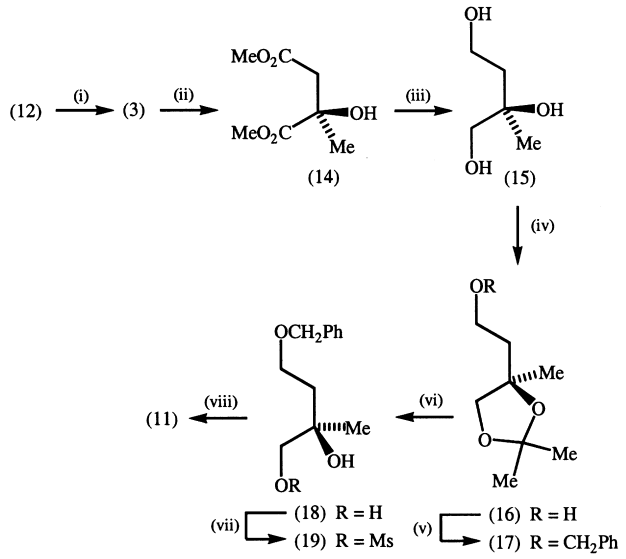


Scheme 2

A great deal of effort has been invested in the synthesis of citramalic acid in monochiral form due to its considerable potential as a chiral building block in organic synthesis.[10] Both enantiomers have been obtained by (i) classical resolution of the isochiral acid,[11] (ii) microbiological methods[10,12] and (iii) enantioselective synthesis.[13] The most efficient synthesis is due to Staring, Moorlag and Wynberg[14] who obtained (*R*)- and (*S*)-citramalic acids (3) and (4), respectively, each in 100% e.e., by hydrolysis of the corresponding (*S*)- and (*R*)-enantiomers (12) and (13) of 4-methyl-4-(trichloromethyl)oxetan-2-one. The oxetanones (12) and (13) are themselves obtained (83% yield, 100% e.e.) by cycloaddition between ketene and 1,1,1-trichloroacetone in the presence of quinine on the one hand and quinidine on the other. Both oxetanones (12) and (13) are commercially available ($7/g from Aldrich©) and they provide, in our opinion, the cheapest source of workable quantities of enantiomerically pure citramalic acid.



* Austrocortilutein numbering. However, under IUPAC recommendations, compound (9) is named as 5,7-dihydroxy-7-methyl-5,6,7,8-tetrahydro-1,4-naphthoquinone.



Scheme 3. (i) NaOH, 5°C, H_2O; (ii) CH_2N_2, CH_2Cl_2/EtOH; (iii) $LiAlH_4$, tetrahydrofuran, 65°C; (iv) acetone, *p*-toluenesulfonic acid, 24 h; (v) $PhCH_2Br$, NaH, Bu_4NI, tetrahydrofuran, 18 h; (vi) 1 M H_2SO_4, tetrahydrofuran, 4 h; (vii) methanesulfonyl chloride, Et_3N, CH_2Cl_2, –10°C, 10 min; (viii) DBU, CH_2Cl_2, 1 h.

*The Synthesis of (1*S*,3*S*)-Austrocortilutein (1)*

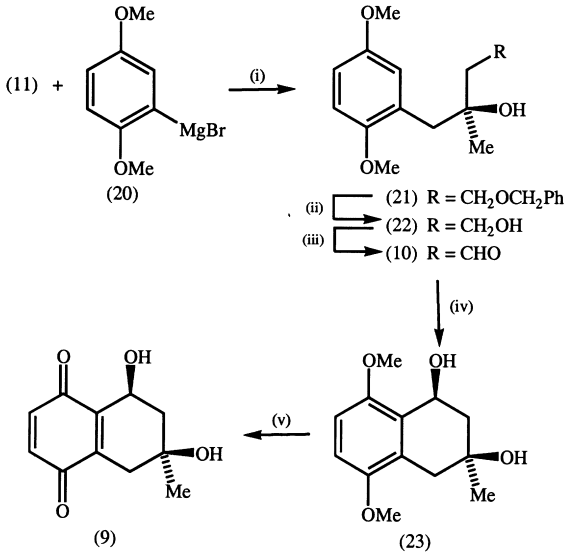
Our route from the (*S*)-oxetanone (12) to the (*R*)-oxiran (11) is summarized in Scheme 3. Thus, (*R*)-citramalic acid (3) was prepared from the (*S*)-oxetanone (12) by Wynberg's method and was esterified with an excess of diazomethane to give dimethyl (*R*)-citramalate (14), $[\alpha]_D$ –28.0 (*c*, 3.3 in $CHCl_3$), in 83% yield from (12). Treatment of the ester (14) with an excess of lithium aluminium hydride in tetrahydrofuran at reflux gave (*R*)-2-methylbutane-1,2,4-triol (15) as a viscous oil, $[\alpha]_D$ +1.5 (*c*, 3.1 in EtOH). The vicinal hydroxy groups of the triol (15) were simultaneously masked as the dioxolan (16), $[\alpha]_D$ +8.8 (*c*, 3.0 in $CHCl_3$), by treatment at room temperature with acetone in the presence of *p*-toluenesulfonic acid during 24 h. It is known that the dioxolan (16) predominates over the corresponding dioxan when this reaction is conducted under conditions of thermodynamic control.[7]

Benzylation of the residual hydroxy group in (16) gave an excellent yield of the (*R*) benzyl ether (17) as a colourless oil, $[\alpha]_D$ +2.4 (*c*, 4.2 in $CHCl_3$), from which the acetal was removed with sulfuric acid. The resulting (*R*) diol (18),* $[\alpha]_D$ –9.3 (*c*, 4.1 in $CHCl_3$), was mesylated selective at the primary hydroxy group by using 1 equiv. of methanesulfonyl chloride at –10°C in dichloromethane containing triethylamine. Under these conditions the (*R*) methanesulfonate (19) was obtained in high yield as a colourless oil, $[\alpha]_D$ +3.9 (*c*, 3.2 in $CHCl_3$). A three-proton singlet at δ 3.02 in the ^1H n.m.r. spectrum of the ester (19) confirmed the presence of the methanesulfonate group, while the downfield shift in the signals due to the C 1 methylene protons [from δ 3.39 and 3.46 in (18) to δ 4.06 in (19)] proves that the ester is a primary mesylate.[15]

Exposure of the mesylate (19) to DBU gave (*R*)-2-methyl-2-[2′-(phenylmethoxy)ethyl]oxiran (11)† as a colourless oil, $[\alpha]_D$ –9.4 (*c*, 3.0 in $CHCl_3$), the structure of which is fully consistent with the spectroscopic data. In particular, the ^1H n.m.r. spectrum shows a two-proton singlet at δ 4.50 and a five-proton multiplet centred at δ 7.32 due to the benzylic and aromatic protons, respectively, while the protons of the C 2 methyl group resonate at δ 1.34 as a doublet (*J* 0.5 Hz) due to long-range coupling with one of the methylene protons at C 3. The diastereotopic methylene protons at C 3 form an AB quartet with components centred at δ 2.60 and δ 2.70 while the protons of the C 1′ and C 2′ methylene groups each give rise to multiplets due to geminal and vicinal couplings.

The chemistry depicted in Scheme 3 and discussed above brings us to what was our first target, the enantiomerically pure oxiran (11);‡ pleasingly, each step proceeds in greater than 80% chemical yield.

The next phase of the synthesis takes us from the (*R*)-oxiran (11) to the pivotal (1*S*,3*S*)-1,3-dihydroxy-1,2,3,4-tetrahydronaphthoquinone (9) (Scheme 4). Accordingly, 2-bromo-1,4-dimethoxybenzene was prepared by bromination of 1,4-dimethoxybenzene with potassium bromide and hydrogen peroxide in the presence of sulfuric acid[16] and subsequently transformed to the corresponding Grignard reagent (20) in standard fashion. Addition of a tetrahydrofuran solution of (20) at –78°C to the oxiran (11) in the pres-



Scheme 4. (i) Dilithium tetrachlorocuprate 0.1 M, tetrahydrofuran, –78°C; (ii) H_2/Pd/C, MeOH; (iii) 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one, H_2O, CH_2Cl_2, 6 h; (iv) $SnCl_4$, –78 to –30°C, 3.5 h; (v) ceric ammonium nitrate, MeCN/H_2O, 5 min.

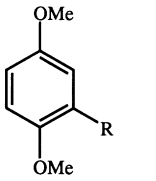
* The (*S*) diol *ent*-(18) was obtained in monochiral form by the same method beginning from the (*R*)-oxetanone (13) (see above); in contrast *ent*-(18) was produced in only 47% e.e. from the benzyl ether of 3-methylbut-3-en-1-ol by treatment with AD-mix-α.[5]

† (±)-(11) is readily available from 3-methylbut-3-en-1-ol by benzylation followed by epoxidation of the olefinic double bond with magnesium monoperoxyphthalate. Most of the subsequent new chemistry was developed using (±)-(11) before being applied to the monochiral series.

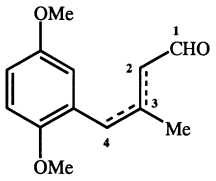
‡ The enantiomeric purity of (11) was confirmed by subsequent transformations that ultimately delivered the natural product (1).

ence of dilithium tetrachlorocuprate gave (*S*)-4-benzyloxy-1-(2′,5′-dimethoxyphenyl)-2-methyl-4-phenoxybutan-2-ol (21) as a colourless oil, $[\alpha]_D$ –7.2 (*c*, 1.9 in $CHCl_3$), in 92% yield. The structure (21) for the product is entirely consistent with the spectroscopic data. Thus, the ^{1}H n.m.r. spectrum contains an AB quartet with components centred at δ 2.73 and 2.82 due to the diastereotopic protons of the C 1 methylene group. A two-proton singlet at δ 4.40 assigned to the benzylic protons of the protecting group and a complex four-proton couplet, with components centred at δ 1.83 and 3.72, accounts for the remaining methylene protons of the side chain. Also present in the sprectrum are methoxy resonances at δ 3.75 and 3.77, a *C*-methyl singlet at δ 1.10 and an envelope of resonances between δ 6.70 and 7.38, which account for eight aromatic protons.

Hydrogenolysis of the benzyl ether group in (21) gave the (*S*) diol (22) as a colourless oil, $[\alpha]_D$ –1.6 (*c*, 2.1 in $CHCl_3$), in quantitative yield. The composition of the important chiral diol (22) was confirmed by combustion analysis and the structure was in full accord with the spectroscopic data (Experimental section). Oxidation of the primary alcohol group in (22) to the corresponding aldehyde (10) in an acceptable yield proved to be a major challenge and several oxidizing agents were investigated before optimum conditions were defined. The best yield of (10) (90%) was obtained by using the Dess–Martin periodinane.[17] The reagent was prepared in the prescribed way and, when this was stirred with the alcohol (22) in wet dichloromethane at room temperature, gave the aldehyde (10), $[\alpha]_D$ +13.5 (*c*, 2.8 in $CHCl_3$). The structure of the aldehyde (10) was confirmed from the ^{1}H n.m.r. spectrum in which the aldehydic proton resonates at δ 9.83 as a triplet (*J* 2.2 Hz) due to vicinal coupling with the protons of the C 2 methylene group. The signals from the methylene protons themselves appear as an AB quartet with components centred at δ 2.45 and 2.55. The carbonyl carbon in (10) resonates at δ 203.2 in the ^{13}C n.m.r. spectrum.



(24) R = CHO
(25) R = CH_2COCH_3



(26) $C^{3,4}$ is C=C
(27) $C^{2,3}$ is C=C

Less successful were attempts to oxidize the alcohol (22) under Swern[18] conditions [50% yield of (10)], by using pyridinium dichromate[19] (37% yield) and with tetrapropylammonium perruthenate[20] (28%). With pyridinium dichromate, the alcohol (22) gave not only the aldehyde (10) but also 16% of 2,5-dimethoxybenzaldehyde (24), the ^{1}H n.m.r. spectrum of which was identical with that of an authentic sample. Similarly, the reaction of (22) with the perruthenate reagent gave, *inter alia*, 1-(2′,5′-dimethoxyphenyl)propan-2-one (25) (12%). The ^{1}H n.m.r. spectrum of (25) contains singlets at δ 2.13 and δ 3.63, due to the C 3 methyl and C 1 methylene protons, respectively, a multiplet between δ 6.70 and δ 6.80, due to the aromatic protons, and two methoxy resonances, at δ 3.72 and δ 3.73. It is possible that the carbonyl compounds (24) and (25) are formed by initial loss of the C 3 hydroxy group (as H_2O) from (10) to give one or other of the alkenes (26) and (27). Subsequent oxidative cleavage of the resulting double bond in (26) would give the aldehyde (24), while analogous cleavage of (27) would give the ketone (25).

Stereospecific cyclisation of the aldehyde (10) to the tetrahydronaphthalene (23) is an important step in our approach to (1*S*,3*S*)-austrocortilutein (1) since it is during this step that the stereochemistry at C 3 is translated to C 1. It was achieved by treatment of the aldehyde (10) with tin(IV) chloride in dichloromethane at –78°C, which gave the (1*S*,3*S*)-diol (23) as a colourless crystalline solid, $[\alpha]_D$ –6.8 (*c*, 2.6 in $CHCl_3$), in 84% yield. The structure and relative stereochemistry of the tetrahydronaphthalene (23) are in full accord with the analytical and spectroscopic data. Thus, combustion analysis and mass spectrometry lead to the molecular formula $C_{13}H_{18}O_4$. In the ^{1}H n.m.r. spectrum there are three-proton singlets at δ 3.79 and 3.85, due to the aromatic methoxy groups, a broad signal between δ 6.71 and 6.81 from two aromatic protons, and characteristic set of signals from the protons of a 3-hydroxy-3-methyltetrahydroaromatic ring. Thus, one of the C 2 protons appears as a double doublet at δ 1.85 (*J* 14.5 and 5.0 Hz) and the other as a double doublet of doublets at δ 2.26 (*J* 14.5, 2.2 and 2.2 Hz). The protons at C 4 appear as a doublet (*J* 17.7 Hz) at δ 2.46 and a double doublet (*J* 17.7 and 2.2 Hz) at δ 3.07. The alcoholic methine proton (H 1) appears as a multiplet at δ 5.17 and the protons of the C 3 methyl group resonate at δ 1.42. The protons at δ 2.26 and 3.07 are w-coupled and can be assigned to $H_{eq}2$ and $H_{eq}4$, respectively, and therefore the signals at δ 1.85 and 2.46 must be due to $H_{ax}2$ and $H_{ax}4$, respectively. The magnitude of the vicinal coupling constants between H 1 and the protons at C 2 ($J \leq 5.0$ Hz) precludes any *trans*-diaxial relationships and places the hydroxy groups at C 1 and C 3 on the same face of the tetrahydroaromatic ring. Since the absolute stereochemistry at C 3 is known to be (*S*), the configuration at C 1 in (23) must also be (*S*). The ^{1}H n.m.r. data discussed above are very similar to the corresponding chemical shifts and coupling constants observed in the spectrum of the natural product (1).[1]

The stereospecificity of the intramolecular Friedel–Crafts reaction of (10) suggests that the Lewis acid chelates to the C 3 hydroxy group and to the carbonyl oxygen in (10), as shown in Fig. 1. Consequently, if carbon–carbon bond formation involves a chair-like transition state then the nucleophile can only attack the *re* face of the aldehyde carbonyl group.

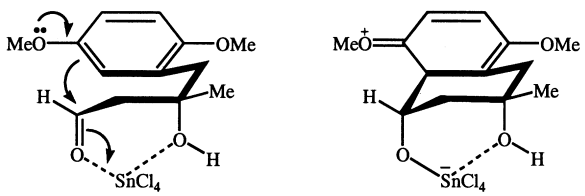


Fig. 1. Lewis acid chelation in the intramolecular Friedel–Crafts reaction of (10).

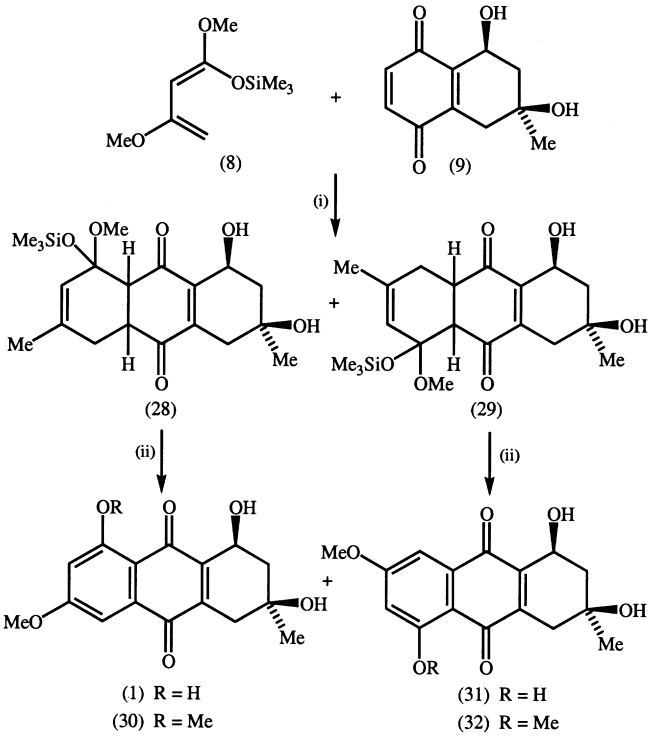
Oxidative demethylation of the tetrahydronaphthalene (23) with ceric ammonium nitrate in aqueous acetonitrile gave (1*S*,3*S*)-1,3-dihydroxy-1,2,3,4-tetrahydronaphthoquinone (9) as a yellow gum, $[\alpha]_D$ –63 (*c*, 0.81 in EtOH), in quantitative yield. High-resolution mass measurement confirmed the molecular formula $C_{11}H_{12}O_4$ and the ^{13}C n.m.r. spectrum contains carbonyl carbons resonances at δ 187.2 and 187.6.

With the important chiral dienophile (9) in hand, the diene (8) necessary for assembly of the C ring in (1*S*,3*S*)-austrocortilutein (1) was prepared from methyl acetoacetate in 62% yield over two steps.[6] To effect the requisite Diels–Alder reaction between (8) and (9) a solution of the two in benzene was stirred at room temperature for 9 h (Scheme 5). We did not attempt to isolate the presumed adducts (28) and (29) but rather added water and stirred the mixture vigorously in the air for 12 h to cause aromatization to a mixture of the corresponding naphthoquinones. At this stage the mixture consisted of the hydroxy quinone (1) and its phenolic methyl ether (30) derived from the adduct (28), and the quinones (31) and (32) arising from the adduct (29). While the ratio of the adducts (28) and (29) is controlled by the regioselectivity of the Diels–Alder reaction, the ratio of the quinones (1) and (30) on the one hand, and (31) and (32) on the other, could vary depending on the conditions employed for aromatization of the original adducts. The products obtained under the conditions described above were separated by preparative thin-layer chromatography into two yellow zones. The more mobile zone (R_F 0.40) consisted of a mixture of (1*S*,3*S*)-austrocortilutein (1) and its regioisomer (31) in a ratio of 4 : 1 and in a combined yield of 40%.* The quinones (1) and (31) could not be separated by using chromatography but they can be differentiated and their relative proportions quantified from the ^1H n.m.r. spectrum of the mixture. Of particular value in this regard are the hydrogen-bonded phenolic hydroxy resonances, which are well resolved at δ 12.20 for (1) and 12.24 for (31).

Likewise, the lower R_F yellow zone (R_F 0.20) consisted of a mixture of the quinone 8-*O*-methyl ethers (30) and (32) that were identified by ^1H n.m.r. spectroscopy. In the case of the reaction described above the ratio of the higher to lower R_F zones (hydroxy quinones to their ethers) was greater than 95 : 5. The methyl ethers (30) and (32) could be demethylated to their counterparts (1) and (31) by using boron trichloride at –78°C but this process was inefficient and was not employed on a routine basis.

Although aerial aromatization of the cycloadducts (28) and (29) was the most efficient in terms of the yield of the natural product (1), other conditions were examined. When exposed to DBU/oxygen the adducts (28) and (29) gave a preponderance of the methyl ethers (30) and (31) (31% isolated yield) over the hydroxy quinones (1) and (31) (4%). With silica gel/oxygen and with DDQ equal amounts of the hydroxy and methoxy quinones resulted (40–50% combined yield). Poor yields (<20%) of the quinones (1) and (31) were recovered from reactions with oxygen under acidic conditions.

As was mentioned above, the tetrahydroanthraquinones (1) and (31) could not be separated by chromatography;



Scheme 5. (i) Benzene, room temp., 9 h; (ii) H_2O, O_2, 12 h.

nevertheless, fractional crystallization of the mixture from chloroform gave (1*S*,3*S*)-austrocortilutein (1) in pure form as orange-yellow needles, m.p. 183–185°C, $[\alpha]_D$ +55 (*c*, 0.10 in $CHCl_3$), in 22% yield from the chiral tetrahydronaphthoquinone (9). Some of the important physical and spectroscopic properties of the synthetic material are compared with those reported[1] for the quinone from *Dermocybe splendida* in Table 1. From this comparison it is clear that both structurally and stereochemically the synthetic and natural samples of (1*S*,3*S*)-austrocortilutein (1) are identical. This is the first report of the total synthesis of the natural product (1) in monochiral form.

The Synthesis of (1S,3S)-Austrocortirubin (2)

(1*S*,3*S*)-Austrocortirubin (2) should be available by Diels–Alder cycloaddition of the (1*S*,3*S*)-tetrahydronaphthoquinone (9) with the known[22] oxygenated diene (33) (Scheme 6). Accordingly, the enol ether of methyl 4-methoxy-3-oxobutanoate was generated, deprotonated, and the enolate so formed was trapped with chlorotrimethylsilane. The resulting diene (33) was obtained in 77% yield as a colourless oil, the ^1H n.m.r. spectrum of which consists of signals from one trimethylsilyl group (δ 0.29), three enolic methyl ether groups (δ 3.56, 3.61 and 3.67), and two olefinic protons (δ 4.46 and 5.82). The diene (33) is stable if stored under nitrogen at –78°C but is prone to decomposition on standing at higher temperatures for longer periods.

When the diene (33) and the chiral quinone (9) were stirred together at room temperature for 18 h (Scheme 6) and

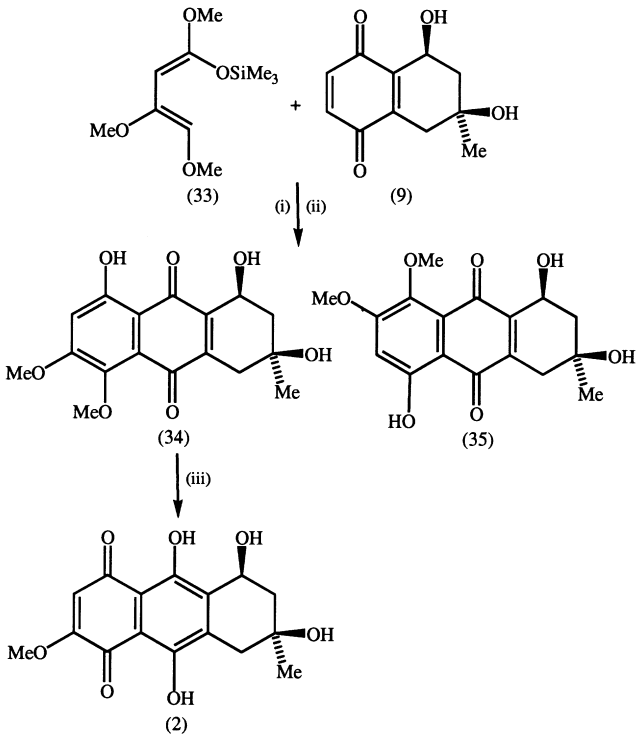
* This ratio was not improved by carrying out the Diels–Alder reaction in the presence of Lewis acids such as tetraacetyl diborate.[21]

Table 1. Some physical and spectroscopic properties of natural and synthetic (1*S*,3*S*)-austrocortilutein (1)

Property	Natural product (1)[1]	Synthetic (1)
M.p. (°C)	183–185	182–185
$[\alpha]_D$	+52 (*c*, 0.095 in $CHCl_3$)	+55 (*c*, 0.10 in $CHCl_3$)
^{1}H n.m.r.[A] δ	1.45 (3H, s, 3-Me) 1.82 (1H, dd, 14.7, 5.1, $H_{ax}2$) 2.30 (1H, ddd, 14.7, 1.8, 1.8, $H_{eq}2$) 2.41 (1H, dd, 19.8, 1.5, $H_{ax}4$) 3.02 (1H, dd, 19.8, 1.8, $H_{eq}4$) 3.06 (1H, s, 3-OH) 3.51 (1H, d, 5.1, 1-OH) 3.91 (3H, s, 6-OMe) 5.08 (1H, m, H 1) 6.65 (1H, d, 2.6, H 7) 7.19 (1H, d, 2.6, H 5) 12.21 (1H, s, 8-OH)	1.45 (3H, s, 3-Me) 1.82 (1H, dd, 14.7, 5.1 Hz, $H_{ax}2$) 2.32 (1H, ddd, 14.7, 1.8, 1.8, $H_{eq}2$) 2.41 (1H, dd, 19.8, 1.5, $H_{ax}4$) 3.01 (1H, dd, 19.8, 1.8, $H_{eq}4$) 3.08 (1H, m, 3-OH) 3.51 (1H, m, 1-OH) 3.91 (3H, s, 6-OMe) 5.08 (1H, m, H 1) 6.64 (1H, d, 2.4, H 7) 7.17 (1H, d, 2.4, H 5) 12.20 (1H, s, 8-OH)
ν_{max} (cm^{-1})	1667, 1639	1665, 1641
m/z (e.i. 15 eV)	304 (55%), 286 (78), 271 (28), 268 (43), 262 (31), 247 (25), 246 (62), 245 (25), 244 (100), 243 (57), 219 (30), 218 (58), 151 (28), 43 (75), 18 (27)	304 (42%), 286 (77), 271 (24), 269 (21), 268 (88), 262 (33), 247 (24), 246 (61), 245 (24), 244 (100), 243 (56), 219 (34), 218 (59), 151 (36), 115 (22)

[A] ^{1}H n.m.r. spectra were recorded in (D)chloroform at 300 and 400 MHz for the natural and synthetic quinones, respectively.

the mixture of adducts so formed was aromatized by adding distilled water and stirring vigorously in air, an orange-red mixture of products was obtained. Preparative thin-layer chromatography gave a major orange-red zone that was composed of a mixture of the tetrahydroanthraquinone (34) and its regioisomer (35) in a ratio of 4 : 1 by ^{1}H n.m.r. spectroscopy. In particular, the spectrum shows clearly resolved,



Scheme 6. (i) Benzene, room temp., 18 h; (ii) H_2O, O_2, 12 h; (iii) BCl_3, CH_2Cl_2, –78°C, 4 h.

hydrogen-bonded phenolic hydroxy signals at δ 13.01 [(34)] and 13.07 [(35)]. The quinones (34) and (35) are coincident by t.l.c. but were separated by fractional crystallization from benzene. In this way the novel tetrahydroanthraquinone 5-*O*-methyl ether (34) was obtained pure as pale red needles, m.p. 175–178°C, $[\alpha]_D$ +15.9 (*c*, 0.27 in $CHCl_3$). The high-resolution mass spectrum of the quinone (34) confirmed the molecular formula $C_{17}H_{18}O_7$ while long-wavelength absorption at 276 and 454 nm in the electronic spectrum accords with a methylated naphthazarin chromophore. The rest of the ^{1}H n.m.r. spectrum of (34) consists of signals from two methoxy groups (δ 3.85 and 3.94), a typically benzenoid aromatic proton (δ 6.65),[23] and the methyl and methylene protons of the tetrahydroaromatic ring. These signals are very similar in chemical shift and multiplicity to those observed in the spectrum of (1*S*,3*S*)-austrocortilutein (2) (Table 2).

Selective removal of the more sterically encumbered 5-*O*-methyl ether from the quinone (34) was achieved by using boron trichloride at –78°C.[24] Workup and chromatography then gave (1*S*,3*S*)-austrocortirubin (2), $[\alpha]_D$ +34 (*c*, 0.54 in $CHCl_3$) {lit.[1] $[\alpha]_D$ +34 (*c*, 0.54 in $CHCl_3$)}, as bright red needles from benzene, identical in all respects (Table 2) with the major red pigment isolated from *Dermocybe splendida*.[1] As the data in Table 2 reveal, the chemical shift of H 7 in the spectrum of quinone (2) is δ 6.21, in line with the tautomer shown, in which the quinone occupies the peripheral ring.

*The Synthesis of (1*R,3R*)-Austrocortilutein (5)*

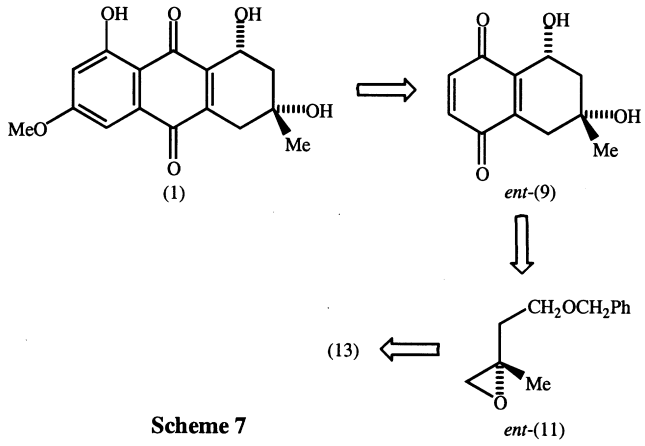
All four stereoisomers of 1,3,8-trihydroxy-6-methoxy-3-methyl-1,2,3,4-tetrahydro-9,10-anthraquinone (austrocortilutein) are known as natural products.[1,25] A synthesis of (1*R*,3*R*)-austrocortilutein (5) based on the chemistry developed above requires, firstly, the preparation of the (1*R*,3*R*)-

Table 2. Selected physical and spectroscopic properties for natural and synthetic (1*S*,3*S*)-austrocortirubin (2)

Property	Natural product (2)[1]	Synthetic (2)
M.p. (°C)	193–195	193–195
$[\alpha]_D$	+34 (*c*, 0.543 in $CHCl_3$)	+34 (*c*, 0.54 in $CHCl_3$)
^{1}H n.m.r.[A] δ	1.48 (3H, s, 3-Me) 1.88 (1H, dd, 14.7, 4.8, $H_{ax}2$) 2.35 (1H, ddd, 14.7, 1.8, 1.8, $H_{eq}2$) 2.59 (1H, d, 19.1, $H_{ax}4$) 3.19 (1H, dd, 19.1, 1.8, $H_{eq}4$) 3.95 (3H, s, OMe) 5.20 (1H, m, H 1) 6.21 (1H, s, H 7) 12.69 (1H, s, OH) 13.32 (1H, s, OH)	1.48 (3H, s, 3-Me) 1.89 (1H, dd, 14.7, 4.8, $H_{ax}2$) 2.35 (1H, ddd, 14.7, 1.8, 1.8, $H_{eq}2$) 2.59 (1H, d, 19.1, $H_{ax}4$) 3.19 (1H, dd, 19.1, 1.8, $H_{eq}4$) 3.95 (3H, s, OMe) 5.21 (1H, m, H 1) 6.21 (1H, s, H 7) 12.69 (1H, s, OH) 13.33 (1H, s, OH)
ν_{max} (cm^{-1})	1600	1608
m/z (e.i. 15 eV)	320 (60%), 304 (12), 303 (17), 302 (100), 300 (18), 287 (24), 285 (18), 284 (89), 260 (37), 259 (36), 245 (30), 244 (54), 242 (14)	320 (92%), 303 (16), 302 (72), 287 (38), 284 (42), 278 (21), 260 (49), 259 (50), 245 (30), 244 (100), 242 (22)

[A] ^{1}H n.m.r. spectra were recorded in (D)chloroform at 300 and 400 MHz for the natural and synthetic quinones, respectively.

tetrahydronaphthoquinone *ent*-(9) (Scheme 7) beginning from the (*R*)-oxetanone (13), and cycloaddition of *ent*-(9) with the diene (8). This chemistry precisely mirrors that described in Schemes 4 and 5 and need only be mentioned briefly here. As expected, the spectroscopic properties of each of the intermediates are identical, with the obvious exception of chiroptical properties, with those obtained earlier for their respective antipodes.



Scheme 7

We described previously a synthesis of the (*S*)-oxiran *ent*-(11) from sodium (*S*)-citramalate.[7] Here, the (*S*)-oxiran *ent*-(11) was obtained more efficiently (and more economically) from the (*R*)-oxetanone (13). Thus, alkaline hydrolysis of (13) and methylation of the intermediate dicarboxylic acid (4) gave dimethyl (*S*)-citramalate, $[\alpha]_D$ +28 (*c*, 3.3 in $CHCl_3$). Reduction to the triol *ent*-(15), $[\alpha]_D$ –1.96 (*c*, 3.3 in $CHCl_3$), and subsequent acetal formation gave the acetonide *ent*-(16), $[\alpha]_D$ –9.0 (*c*, 2.9 in $CHCl_3$). Benzylation gave the (*S*) benzyl ether *ent*-(17), $[\alpha]_D$ –2.8 (*c*, 3.8 in $CHCl_3$), which on hydrolysis gave the (*S*) diol *ent*-(18), $[\alpha]_D$ +9.3 (*c*, 4.1 in $CHCl_3$). Mesylation of *ent*-(18) and treatment of the resulting ester *ent*-(19), $[\alpha]_D$ –3.8 (*c*, 3.2 in $CHCl_3$), with DBU gave (*S*)-oxiran *ent*-(11), $[\alpha]_D$ +9.6 (*c*, 3.0 in $CHCl_3$), as a colourless oil. Treatment of *ent*-(11) with the Grignard reagent (20) gave (*R*)-4-benzyloxy-1-(2′,5′-dimethoxyphenyl)-2-methylbutan-2-ol *ent*-(21), $[\alpha]_D$ +7.0 (*c*, 2.0 in $CHCl_3$), which after catalytic hydrogenolysis and treatment of the resulting (*S*) diol *ent*-(22) {$[\alpha]_D$ +1.6 (*c*, 2.1 in $CHCl_3$)} with the Dess–Martin periodinane gave the aldehyde *ent*-(10), $[\alpha]_D$ –13.3 (*c*, 2.8 in $CHCl_3$), in 88% yield. Cyclization of *ent*-(10) in the presence of stannic chloride gave the (1*R*,3*R*)-tetrahydronaphthalenediol *ent*-(23), $[\alpha]_D$ +7.1 (*c*, 2.6 in $CHCl_3$). Oxidative demethylation of *ent*-(23) afforded the new (1*R*,3*R*)-naphthoquinone *ent*-(9), $[\alpha]_D$ +62 (*c*, 0.80 in EtOH), which underwent a regioselective Diels–Alder cycloaddition reaction with the diene (8) in benzene. *In situ* aerial oxidation of the cycloadducts gave a mixture of (1*R*,3*R*)-austrocortilutein (5) and its regioisomer (36) in a 4 : 1 ratio (by ^{1}H n.m.r. spectroscopy). Fractional crystallization of the mixture from methanol gave (1*R*,3*R*)-austrocortilutein (5) as bright orange-red needles, m.p. 183–186°C, $[\alpha]_D$ –63 (*c*, 0.24 in EtOH) {lit.[25] $[\alpha]_D$ –61 (*c*, 0.24 in EtOH)}, which was indistinguishable in all respects (Table 3) from the natural product (5) isolated from *Dermocybe* sp. WAT 21568.[25]

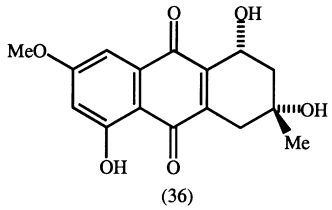


Table 3. Some physical and spectroscopic properties for natural and synthetic (1*R*,3*R*)-austrocortirubin (5)

Property	Natural product (5)[25]	Synthetic (5)
M.p. (°C)	183–187	183–186
$[\alpha]_D$	–61 (*c*, 0.24 in EtOH)	–63 (*c*, 0.24 in EtOH)
^{1}H n.m.r.[A] δ	1.43 (3H, s, 3-Me) 1.78 (1H, dd, 14.6, 5.1, $H_{ax}2$) 2.27 (1H, ddd, 14.6, 2.2, 1.9, $H_{eq}2$) 2.37 (1H, dd, 19.9, 1.9, $H_{ax}4$) 2.99 (1H, dd, 19.9, 2.2, $H_{eq}4$) 3.30 (1H, br s, 3-OH) 3.71 (1H, d, 5.1, 1-OH) 3.88 (3H, s, 6-OMe) 5.04 (1H, m, H 1) 6.58 (1H, d, 2.6, H 7) 7.09 (1H, d, 2.6, H 5) 12.19 (1H, s, 8-OH)	1.45 (3H, s, 3-Me) 1.81 (1H, dd, 14.5, 5.1 Hz, $H_{ax}2$) 2.29 (1H, ddd, 14.7, 2.2, 2.2, $H_{eq}2$) 2.40 (1H, dd, 19.8, 1.5, $H_{ax}4$) 3.01 (1H, dd, 19.8, 2.2, $H_{eq}4$) 3.07 (1H, br s, 3-OH) 3.49 (1H, m, 1-OH) 3.91 (3H, s, 6-OMe) 5.07 (1H, m, H 1) 6.64 (1H, d, 2.6, H 7) 7.18 (1H, d, 2.6, H 5) 12.21 (1H, s, 8-OH)
ν_{max} (cm^{-1})	1667, 1639	1659, 1642
m/z (e.i. 15 eV)	304 (55%), 286 (78), 271 (28), 268 (43), 262 (31), 247 (25), 246 (62), 245 (25), 244 (100), 243 (57), 219 (30), 218 (58), 151 (28), 43 (75), 18 (27)	304 (42%), 286 (77), 271 (24), 269 (21), 268 (88), 262 (33), 247 (24), 246 (61), 245 (24), 244 (100), 243 (56), 219 (34), 218 (59), 151 (36), 115 (22)

[A] ^{1}H n.m.r. spectra were recorded in (D)chloroform at 300 and 400 MHz for the natural and synthetic quinones, respectively.

Conclusions

The synthesis of the naturally occurring, biologically active tetrahydroanthraquinones (1), (2) and (5), each in monochiral form, is described for the first time. The method focuses on the chiral tetrahydronaphthoquinone dienophiles (9) and *ent*-(9), which are prepared from the commercially available oxetanones (12) and (13), respectively, via the corresponding enantiomers of citramalic acid. In principle, the method is applicable to a wide range of (1*S*,3*S*)- and (1*R*,3*R*)-1,3-dihydroxy-1,2,3,4-tetrahydroanthraquinones by changing the diene used in the Diels–Alder cycloaddition step. Extension of the methodology described herein to *trans*-1,3-dihydroxytetrahydroanthraquinone systems is described in earlier parts of this series.[26]

Experimental

General Methods And Materials

Where compounds have been prepared in both isochiral and monochiral form by the same procedure, details are described only for experiments in the optically active series. In those cases where the data from the isochiral compounds differ from those of their enantiomerically pure counterparts, the pertinent data for the former are listed in square brackets. In those cases where both enantiomers of a compound are synthesized, the procedure is described for only one enantiomer and the specific rotation of the enantiomer is listed in brackets.

All reactions were performed in oven-dried (140°C) glassware under a positive pressure of dry nitrogen. After workup, organic solvents were dried ($MgSO_4$ or Na_2SO_4) and removed under reduced pressure. Analytical thin-layer chromatography (t.l.c.) was performed on Merck precoated plates (0.25 mm, Kieselgel 60 GF_{254}) and visualized both in daylight and under short (254 nm) and long (360 nm) wavelength ultraviolet light. Colourless compounds on t.l.c. were exposed to phosphomolybdic acid (5% w/v solution in propan-2-ol) followed by heating at 130°C. Flash pad chromatography[27] and flash chromatography[28] employed Merck Kieselgel 60 silica gel. Preparative thin-layer chromatography was performed on Merck Kieselgel 60 GF_{254} on 20 by 20 cm glass plates (20 g/plate). Gel permeation chromatography was carried out by using columns of Sephadex LH-20 (Pharmacia) suspended and eluted with dichloromethane/methanol (1 : 1).

All solvents were redistilled prior to use; tetrahydrofuran and benzene were distilled from potassium benzophenone ketyl immediately prior to use. Other solvents and reagents were purified by using published procedures.[29] Light petroleum refers to the hydrocarbon fraction boiling in the range 40–60°C.

Equipment

Elemental analyses were performed by Chemical and Micro Analytical Services Pty Ltd, North Essendon, Victoria 3041. Melting points were determined on a Kofler hot stage and are uncorrected. Specific rotations were measured on a Perkin–Elmer 241 MC polarimeter; concentrations refer to solutions in chloroform unless otherwise designated. Ultraviolet spectra were obtained with a Perkin–Elmer Lamda 2 spectrophotometer by using 10 mm quartz cells for solutions in ethanol. Infrared spectra were obtained as potassium bromide disks (solids) or between sodium chloride plates (oils) by using Perkin Elmer 983G Grating or 1600 series Fourier-transform spectrophotometers. N.m.r. spectra were recorded with JEOL JNM-GX-400 (399.65 MHz, ^{1}H; 100.4 MHz, ^{13}C), VARIAN UNITY 300 (299.95 MHz, ^{1}H; 75.43 MHz, ^{13}C), JEOL JNM-FX-100 (99.55 MHz, ^{1}H; 25.00 MHz, ^{13}C) and JEOL JNM-FX-90Q (89.55 MHz, ^{1}H; 22.50 MHz, ^{13}C) spectrometers, for solutions in (D)chloroform unless indicated otherwise. Electron impact mass spectra were obtained with a V.G. Micromass 7070F spectrometer operating at 70 eV unless indicated otherwise. The mass of each ion is given followed by its relative abundance. In general, only peaks of relative abundance greater than 20% of the base peak are quoted.

Dimethyl (R)-*Citramalate (14)*

A solution of sodium hydroxide (10 M, 40 ml) was added dropwise to a suspension of the (*S*)-oxetanone (12) (14.0 g, 69.0 mmol) in water (70 ml) at 5°C. The mixture was stirred at room temperature for 18 h, acidified to pH 1 with concentrated hydrochloric acid (10 M) and evaporated under reduced pressure. The crude acid (3) was extracted from

the residue with warm ethyl acetate (4 × 80 ml). Benzene (50 ml) was added to the combined extract and evaporation of the solvents gave (*R*)-citramalic acid (3) as a viscous oil (9.30 g, 91%), which was not purified further. The diacid (3) was dissolved in dichloromethane/ethanol (2.5 : 1) (400 ml) and diazomethane [prepared *in situ* by the dropwise addition of concentrated aqueous sodium hydroxide to Diazald© (52.0 g, 243 mmol)][30] was bubbled into the solution over 30 min. Excess diazomethane was destroyed by the dropwise addition of glacial acetic acid, toluene (40 ml) was added and the solvent was evaporated. Distillation of the residue gave dimethyl (*R*)-citramalate (14) [10.02 g, 83% from (12)] as a colourless oil, b.p. 80–100°C/2 mmHg; $[\alpha]_D$ –28 (*c*, 3.3) {(*S*) *ent*-(14) $[\alpha]_D$ +28.0 (*c*, 3.3), lit.[7] $[\alpha]_D$ +27.8 (*c*, 2.20)}. ν_{max} 3504, 2953, 1733, 1435 cm^{-1}. δ_H (300 MHz) 1.42 (3H, s, 2-Me), 2.66 (1H, d, *J* 16.4 Hz, H 3), 2.96 (1H, d, *J* 16.4 Hz, H′3), 3.67 and 3.78 (each 3H, s, OMe). δ_C (75 MHz) 26.2, 44.0, 51.8, 52.9, 72.5, 171.3, 175.9. *m/z* (40 eV) 145 ([M–31]$^+$, 1%), 117 (49), 85 (39), 43 (100).

(R)-*2-Methylbutane-1,2,4-triol (15)*

A solution of dimethyl (*R*)-citramalate (14) (5.28 g, 30.0 mmol) in tetrahydrofuran (20 ml) was added dropwise with stirring to a solution of lithium aluminium hydride (3.76 g, 100 mmol) in tetrahydrofuran (150 ml). When evolution of hydrogen had ceased, the mixture was heated at reflux for 18 h, cooled to 0°C and the excess reducing agent was destroyed by the successive addition of water (4 ml), aqueous sodium hydroxide (2.5 M, 6 ml), and a further aliquot of water (10 ml). After stirring for 1 h at room temperature, the mixture was filtered and the filter cake was washed with tetrahydrofuran (200 ml) and absolute ethanol (200 ml). The filtrate and washings were combined and evaporated. The residue was passed through a short column of silica gel with methanol/dichloromethane (9 : 1) as eluent to afford the (*R*) triol (15) (3.03 g, 84%) as a viscous oil, b.p. 130–140°C/0.1 mmHg; $[\alpha]_D$ +1.5 (*c*, 3.1 in EtOH) {(*S*) *ent*-(15) $[\alpha]_D$ –1.96 (*c*, 3.3 in EtOH), lit.[7] $[\alpha]_D$ –1.5 (*c*, 3.07 in EtOH)}. ν_{max} 3348, 2935, 1377, 1127, 1054 cm^{-1}. δ_H [90 MHz, (D_4)methanol] 1.16 (3H, s, 2-Me), 1.74 (2H, t, *J* 6.8 Hz, $H_2$3), 3.37 (2H, s, $H_2$1), 3.72 (2H, t, *J* 6.8 Hz, $H_2$4). δ_C [75 MHz, (D_4)methanol] 24.4, 41.4, 59.2, 70.5, 73.4. *m/z* (40 eV) 89 ([M–CH_2OH]$^+$, 11%), 71 (23), 43 (100), 18 (86).

(R)-*2,2,4-Trimethyl-1,3-dioxolan-4-ethanol (16)*

To a stirred solution of the (*R*) triol (15) (1.49 g, 12.4 mmol) in acetone (50 ml) was added *p*-toluenesulfonic acid (30 mg). The solution was stirred at room temperature for 24 h and neutralized with sodium hydrogen carbonate (1.0 g). The suspension was stirred for 30 min, filtered and the filtrate was concentrated under reduced pressure. Flash chromatography of the residue with ether/light petroleum (85 : 15) as eluent gave (*R*)-2,2,4-trimethyl-1,3-dioxolan-4-ethanol (16) (1.62 g, 82%) as a colourless oil, b.p. 60–70°C/0.1 mmHg; $[\alpha]_D$ +8.8 (*c*, 3.0) {(*S*) *ent*-(16) $[\alpha]_D$ –9.0 (*c*, 2.9) lit.[7] $[\alpha]_D$ –8.9 (*c*, 2.82)}. ν_{max} 3432, 2981, 1370, 1245, 1214, 1113, 1056 cm^{-1}. δ_H (400 MHz) 1.35 (3H, s, 4-Me), 1.41 and 1.42 (each 3H, br s, 2,2-Me_2), 1.74 (1H, ddd, *J* 14.4, 6.0, 4.0 Hz, H β), 1.92 (1H, ddd, *J* 14.4, 8.3, 4.6 Hz, H β), 2.53 (1H, br s, OH), 3.77 (1H, ddd, *J* 11.2, 6.0, 4.6 Hz, H α), 3.79 (1H, d, *J* 8.5 Hz, H 5), 3.86 (1H, d, *J* 8.5 Hz, H 5), 3.90 (1H, ddd, *J* 11.2, 8.3, 4.0 Hz, H α). δ_C (22.5 MHz) 24.8, 26.8, 27.0, 41.0, 59.2, 74.5, 81.2, 109.4. *m/z* (15 eV) 145 ([M–Me]$^+$, 100%), 115 (51), 85 (84), 72 (24), 43 (24).

(R)-*2,2,4-Trimethyl-4-[2′-(phenylmethoxy)ethyl]-1,3-dioxolan (17)*

A solution of the alcohol (16) (2.15 g, 13.4 mmol) in tetrahydrofuran (20 ml) was added dropwise to a stirred suspension of sodium hydride (0.65 g, 60% dispersion in mineral oil, 16 mmol) in tetrahydrofuran (30 ml). To the resulting grey suspension was added tetrabutylammonium iodide (50 mg, 0.14 mmol) followed by benzyl bromide (2.52 g, 14.7 mmol). The mixture was stirred for 24 h, diluted with cold water (60 ml) and extracted into ether (3×50 ml). The combined extract was washed with brine (3×20 ml), dried and concentrated under reduced pressure. Flash chromatography of the residue with dichloromethane/ether (9 : 1) as eluent gave the (*R*)-1,3-dioxolan (17) (3.07 g, 91%) as a colourless oil, b.p. 65–75°C/0.05 mmHg; $[\alpha]_D$ +2.4 (*c*, 4.2) {(*S*) *ent*-(17) $[\alpha]_D$ –2.8 (*c*, 3.8), lit.[7] $[\alpha]_D$ –2.9 (*c*, 3.88)}. ν_{max} 2982, 1495, 1368, 1245, 1212, 1114, 1057 cm^{-1}. δ_H (100 MHz) 1.28 (3H, s, 4-Me), 1.36 and 1.40 (each 3H, s, 2,2-Me_2), 1.92 (2H, t, *J* 6.7 Hz, $H_2$1′), 3.59 (2H, t, *J* 6.7 Hz, $H_2$2′), 3.71 (1H, d, *J* 8.5 Hz, H 5), 3.91 (1H, d, *J* 8.5 Hz, H 5), 4.49 (2H, s, C**H**$_2$Ph), 7.32 (5H, m, ArH). δ_C (75 MHz) 25.0, 26.9, 27.2, 39.5, 66.7, 73.1, 74.3, 80.1, 108.8, 127.5, 127.6, 128.3, 138.3. *m/z* (40 eV) 235 ([M–Me]$^+$, 42%), 192 (36), 91 (100), 43 (51).

(R)-*2-Methyl-4-(phenylmethoxy)butane-1,2-diol (18)*

A solution of the acetonide (17) (2.55 g, 10.2 mmol) in tetrahydrofuran (25 ml), water (4 ml) and aqueous sulfuric acid (1 M, 20 ml) was stirred at 40°C for 4 h. After neutralization with aqueous sodium hydroxide (1 M), the products were extracted into ether (4×60 ml). The combined extract was washed with brine (3×40 ml), dried and evaporated. Flash pad chromatography of the residue using a gradient solvent system (ether/ethyl acetate) gave the (*R*) diol (18) (1.98 g, 92%) as a viscous oil, b.p. 165–175°C/0.6 mmHg; $[\alpha]_D$ –9.3 (*c*, 4.1) {(*S*) *ent*-(18) $[\alpha]_D$ +9.3 (*c*, 4.1), lit.[7] $[\alpha]_D$ +9.5 (*c*, 4.0)}. ν_{max} 3405, 2869, 1454, 1366, 1096, 1056 cm^{-1}. δ_H (400 MHz) 1.18 (3H, s, 2-Me), 1.71 (1H, ddd, *J* 15.0, 6.3, 3.4 Hz, H 3), 1.97 (1H, ddd, *J* 15.0, 8.8, 3.8 Hz, H 3), 3.39 (1H, d, *J* 11.2 Hz, H 1), 3.46 (1H, d, *J* 11.2 Hz, H 1), 3.65 (1H, ddd, *J* 9.8, 6.3, 3.8 Hz, H 4), 3.76 (1H, ddd, *J* 9.8, 8.8, 3.4 Hz, H 4), 4.43 (2H, s, C**H**$_2$Ph), 7.29–7.38 (5H, m, ArH). δ_C (75 MHz) 24.2, 37.8, 66.8, 70.0, 72.4, 73.4, 127.8, 128.4, 137.4. *m/z* (15 eV) 161 ([M–49]$^+$, 35%), 108 (100), 107 (26), 91 (30), 85 (90), 58 (25).

(R)-*2-Hydroxy-2-methyl-4-(phenylmethoxy)butyl Methanesulfonate (19)*

Methanesulfonyl chloride (790 μl, 10.2 mmol) was added over 5 min to a stirred solution of the (*R*) diol (18) (2.15 g, 10.2 mmol) and triethylamine (2.14 ml, 15.3 mmol) in dichloromethane (15 ml) at –10°C. The mixture was stirred for a further 10 min and diluted with dichloromethane (40 ml). The organic phase was washed successively with cold water (2×30 ml), cold hydrochloric acid (1 M, 2×30 ml), saturated aqueous sodium hydrogen carbonate (2×30 ml), brine (2×30 ml), dried and concentrated under reduced pressure. Flash pad chromatography with ether as eluent gave the (*R*) mesylate (19) (2.82 g, 91%) as a viscous colourless oil; $[\alpha]_D$ +3.9 (*c*, 3.2) {(*S*) *ent*-(19) $[\alpha]_D$ –3.8 (*c*, 3.2), lit.[7] $[\alpha]_D$ –3.8 (*c*, 3.23)}. ν_{max} 3325, 2982, 1453, 1368, 1212, 1114, 1057, 1028, 983, 864, 736 cm^{-1}. δ_H [90 MHz, (D_4)methanol] 1.24 (3H, s, 2-Me), 1.85 (2H, t, *J* 6.5 Hz, $H_2$3), 3.02 (3H, s, SO_2Me), 3.66 (2H, t, *J* 6.5 Hz, $H_2$4), 4.06 (2H, s, $H_2$1), 4.49 (2H, s, C**H**$_2$Ph), 7.32 (5H, br s, ArH). δ_C [22.5 MHz, (D_4)methanol] 24.3, 37.1, 38.9, 67.1, 71.5, 74.1, 77.2, 128.7, 128.9, 139.6. *m/z* (15 eV) 289 ([M+1]$^+$, 1.8%), 164 (44), 108 (33), 107 (94), 105 (100), 92 (81), 85 (26), 77 (41).

(R)-*2-Methyl-2-[2′-(phenylmethoxy)ethyl]oxiran (11)*

1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (1.98 ml, 13.2 mmol) in dichloromethane (10 ml) was added to a solution of the mesylate (19) (3.28 g, 11.4 mmol) in dichloromethane (15 ml) and the solution was stirred at room temperature for 1 h. The solution was diluted with dichloromethane (40 ml) and the organic phase was washed successively with cold hydrochloric acid (5%, 2×30 ml), cold saturated aqueous sodium hydrogen carbonate (2×30 ml) and brine (2×30 ml) and the solvent was dried and evaporated. Flash pad chromatography with ether/light petroleum (1 : 1) as eluent gave the (*R*)-oxiran (11) (2.05 g, 94%) as a colourless oil, b.p. 110–120°C/0.4 mmHg; $[\alpha]_D$ –9.4 (*c*, 3.0) {(*S*) *ent*-(11) $[\alpha]_D$ +9.6 (*c*, 3.0), lit.[7] $[\alpha]_D$ +9.6 (*c*, 2.95)}. ν_{max} 2861, 1453, 1105, 738, 698 cm^{-1}. δ_H (400 MHz) 1.34 (3H, d, *J* 0.5 Hz, 2-Me), 1.85 (1H, ddd, *J* 14.4, 6.6, 6.6 Hz, H 1′), 1.95 (1H, dddd, *J* 14.4, 6.2, 6.2, 0.7 Hz, H 1′), 2.60 (1H, dd, *J* 4.9, 0.5 Hz, H 3), 2.70 (1H, dd, *J* 4.9, 0.5 Hz, H 3), 3.55 (1H, ddd, *J* 9.5, 6.6, 6.2 Hz, H 2′), 3.59 (1H, ddd, *J* 9.5, 6.6, 6.2 Hz, H 2′), 4.50 (2H, s, C**H**$_2$Ph), 7.27–7.37 (5H, m, ArH). δ_C (75 MHz) 21.5, 36.6, 54.0, 55.4, 66.6, 73.0, 127.6, 128.4, 138.2. *m/z* (40 eV) 192 (M$^+$, 1.2%), 91 (37), 43 (100).

(±)-*2-Methyl-2-[2′-(phenylmethoxy)ethyl]oxiran* (±)-*(11)*

Benzyl bromide (100 g, 0.585 mol) was added dropwise over 30 min to an ice-cold suspension of 3-methylbut-3-en-1-ol (51.0 g, 0.592 mol),

sodium hydride (35.6 g, 60% dispersion in mineral oil, 0.890 mol), and tetrabutylammonium iodide (1.8 g, 4.9 mmol) in dry tetrahydrofuran (500 ml). The mixture was allowed to stir at room temperature for 16 h and carefully diluted with ice-cold water (300 ml), extracted with ether (3×300 ml), and the combined extract was washed with brine (2×300 ml), dried and evaporated. Distillation of the residue afforded 2-methyl-4-phenylmethoxybut-1-ene (89.5 g, 87%) as a colourless oil, b.p. 100–103°C/12 mmHg (lit.[31] 120–123°C/16 mmHg). ν_{max} 2935, 1649, 1452, 1360, 1102, 736, 697 cm^{-1}. δ_H (400 MHz) 1.76 (3H, s, 2-Me), 2.36 (2H, t, *J* 6.8 Hz, $H_2$3), 3.59 (2H, t, *J* 6.8 Hz, $H_2$4), 4.54 (2H, s, C**H**$_2$Ph), 4.78 (2H, m, $H_2$1), 7.27–7.36 (5H, m, ArH). δ_C (100 MHz) 22.7, 37.8, 68.7, 72.9, 111.5, 127.5, 127.6, 128.3, 138.4, 142.9. *m/z* (15 eV) 176 (M^+, 8.1%), 107 (31), 70 (100). A mixture of 2-methyl-4-phenylmethoxybut-1-ene (10.0 g, 56.7 mmol) and magnesium monoperoxyphthalate[32] (21.0 g, 80 %, 34.0 mmol) in propan-2-ol/water (1 : 1) (300 ml) was stirred at room temperature for 24 h. Sodium hydroxide (2.5 M, 200 ml) was added and the products were extracted into chloroform (5×150 ml), dried and evaporated. Flash pad chromatography of the residue using a gradient solvent system of light petroleum/ether gave the oxiran (±)-(11) (7.0 g, 64%) as a colourless oil that, specific rotation aside, was identical to the material described above.

Sharpless Asymmetric Dihydroxylation[7] of 2-Methyl-4-phenylmethoxybut-1-ene

(±)-2-Methyl-4-phenylmethoxybut-1-ene (182 mg, 1.03 mmol) was added to a stirred mixture of AD-mix-α (1.40 g), t-butyl alcohol (5 ml) and water (5 ml) at 0°C. The suspension was stirred at 0°C for 24 h and sodium sulfite (1.5 g) was added. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. The products were extracted into ethyl acetate (3×10 ml), and the combined extracts were dried and evaporated. Flash pad chromatography of the residue using a gradient solvent system of light petroleum/ether followed by distillation gave optically active (*S*)-2-methyl-4-(phenylmethoxy)butane-1,2-diol *ent*-(18) (155 mg, 72%) {$[\alpha]_D$ +4.4 (*c*, 4.0)}. The specific rotation, when compared with that of a sample of enantiomerically pure *ent*-(18) (see above), corresponds to an e.e. of 47% for the product described here.

2,5-Dimethoxyphenylmagnesium Bromide (20)

To a stirred solution of potassium bromide (26.7 g, 224 mmol) and 1,4-dimethoxybenzene (30.0 g, 210 mmol) in a mixture of water (150 ml) and ethanol (300 ml) was added sulfuric acid (10 M, 38 ml). The solution was heated (gently) to reflux before hydrogen peroxide (90 ml, 30%) was added dropwise over 30 min. After a further 45 min at reflux, water (150 ml) was added to the hot mixture, which was then allowed to stand at room temperature overnight. The solution was decanted and the solvent was evaporated. The residue was extracted with ethyl acetate (3×200 ml) and the combined extracts were washed with dilute sodium thiosulfate (3×200 ml), water (200 ml), dried and evaporated. Flash pad chromatography of the residue using a gradient solvent system of ether/light petroleum followed by distillation gave 2-bromo-1,4-dimethoxybenzene (30.1 g, 62%) as a colourless oil, b.p. 107°C/0.2 mmHg (lit.[16] 164–166°C/55 mmHg). ν_{max} 2942, 1270, 1213, 667 cm^{-1}. δ_H (400 MHz) 3.76 and 3.84 (each 3H, s, OMe), 6.82 (1H, dd, *J* 8.8, 2.6 Hz, H 5), 6.85 (1H, d, *J* 8.8 Hz, H 6), 7.29 (1H, d, *J* 2.6 Hz, H 3). δ_C (100 MHz) 55.8, 56.8, 111.9, 112.8, 113.6, 118.9, 150.2, 154.0. *m/z* 218 ($[M+2]^+$, 96%), 216 (M^+, 95), 203 (99), 201 (100), 107 (27), 79 (28), 63 (21), 28 (36).

A solution of 2-bromo-1,4-dimethoxybenzene (3.19 g, 14.7 mmol) in tetrahydrofuran (15 ml) was added gradually, with stirring, to activated (I_2) magnesium turnings (360 mg, 14.8 mmol) and the mixture was heated at reflux for 4 h then cooled to room temperature.

(S)-*4-Benzyloxy-1-(2′,5′-dimethoxyphenyl)-2-methylbutan-2-ol (21)*

The Grignard reagent (20) was added dropwise to a stirred solution of the (*R*)-oxiran (11) (2.17 g, 11.3 mmol) in tetrahydrofuran (15 ml) containing a catalytic amount of dilithium tetrachlorocuprate (0.1 M, 1.0 ml, 0.10 mmol) at –78°C. The mixture was allowed to warm slowly to room temperature and then stirred for 18 h. The reaction mixture was quenched with saturated aqueous ammonium chloride (30 ml) and the organic phase was extracted into ether (3×70 ml). The combined extract was washed with saturated aqueous sodium hydrogen carbonate (3×60 ml), brine (3×60 ml), water (80 ml), dried and concentrated under reduced pressure. Flash pad chromatography of the residue using a gradient solvent system of ether/light petroleum gave the (*S*)-tertiary alcohol (21) (3.43 g, 92%) as a colourless *oil*, b.p. 200–210°C/0.25 mmHg (Found: C, 72.8; H, 8.0. $C_{20}H_{26}O_4$ requires C, 72.7; H, 7.9%). $[\alpha]_D$ –7.2 (*c*, 1.9) {(*R*) *ent*-(21) $[\alpha]_D$ +7.0 (*c*, 2.0)}. ν_{max} 3499, 2936, 1497, 1222 cm^{-1}. δ_H (300 MHz) 1.10 (3H, s, 2-Me), 1.77–1.89 (2H, m, $H_2$3), 2.73 (1H, d, *J* 13.4 Hz, H 1), 2.82 (1H, d, *J* 13.4 Hz, H 1), 3.70–3.74 (2H, m, $H_2$4), 3.75 and 3.77 (each 3H, s, OMe), 4.40 (2H, s, C**H**$_2$Ph), 6.70–6.81 (3H, m, ArH), 7.26–7.38 (5H, m, CH_2**Ph**). δ_C (100 MHz) 26.8, 40.6, 42.5, 55.6, 55.8, 67.3, 72.8, 73.2, 111.3, 111.8, 118.7, 127.5, 127.6, 127.7, 128.3, 138.1, 151.8, 153.3. *m/z* (15 eV) 330 (M^+, 3.7%), 312 (52), 179 (100), 164 (24), 152 (54), 91 (25).

(S)-*4-(2′,5′-Dimethoxyphenyl)-3-methylbutane-1,3-diol (22)*

A solution of the benzyl ether (21) (1.24 g, 3.75 mmol) in methanol (30 ml) was exposed to hydrogen in the presence of 10% palladium-on-charcoal (120 mg) for 12 h. The mixture was diluted with ethyl acetate (100 ml) and the catalyst was filtered off using a pad of Celite© and the residue was washed thoroughly with ethyl acetate. The filtrate was concentrated under reduced pressure and the residue was distilled to give the (*S*) diol (22) (874 mg, 97%) as a colourless *oil*, b.p. 165–175°C/0.3 mmHg (Found: C, 64.9; H, 8.4. $C_{13}H_{20}O_4$ requires C, 65.0; H, 8.4%). $[\alpha]_D$ –1.6 (*c*, 2.1) {(*R*) *ent*-(22) $[\alpha]_D$ +1.6 (*c*, 2.1)}. ν_{max} 3401, 2934, 1499, 1222, 1024 cm^{-1}. δ_H (400 MHz) 1.20 (3H, s, 3-Me), 1.65 (1H, ddd, *J* 14.4, 5.7, 3.5 Hz, H 2), 1.85 (1H, ddd, *J* 14.4, 9.1, 4.4 Hz, H 2), 2.78 (1H, d, *J* 13.7 Hz, H 4), 2.95 (1H, d, *J* 13.7 Hz, H 4), 3.76 and 3.80 (each 3H, s, OMe), 3.82 (1H, ddd, *J* 11.2, 5.7, 4.4 Hz, H 1), 3.95 (1H, ddd *J* 11.2, 9.1, 3.5 Hz, H 1), 6.69–6.84 (3H, m, ArH). δ_C (100 MHz) 26.4, 42.4, 43.8, 55.6, 56.0, 59.8, 74.8, 111.6, 111.9, 118.9, 126.9, 151.5, 153.6. *m/z* 240 (M^+, 2.9%), 152 (100), 137 (65), 71 (28), 43 (57), 28 (20).

(S)-*4-(2′,5′-Dimethoxyphenyl)-3-hydroxy-3-methylbutanal (10)*

(i) *Dess–Martin periodinane*. A solution of the Dess–Martin periodinane (1.12 g, 2.63 mmol) in dichloromethane (45 ml) was added dropwise to a vigorously stirred solution of the alcohol (22) (420 mg, 1.75 mmol) and water (48 μl, 2.7 mmol) in dichloromethane (45 ml) over 20 min. The cloudy mixture was stirred at room temperature for 6 h and poured into water (50 ml) saturated with sodium hydrogen carbonate and containing sodium thiosulfate (2.35 g). The organic phase was separated and washed with saturated sodium hydrogen carbonate (2×40 ml), water (2×40 ml), dried and evaporated. Distillation of the residue gave the (*S*)-butanal (10) (376 mg, 90%) as a colourless *oil*, b.p. 145–155°C/0.25 mmHg (Found: C, 64.8; H, 7.6. $C_{13}H_{18}O_4$ requires C, 65.5; H, 7.6%). $[\alpha]_D$ +13.5 (*c*, 2.8) {(*R*) *ent*-(10) $[\alpha]_D$ –13.3 (*c*, 2.8)}. ν_{max} 3473, 2929, 1714, 1498, 1222, 1046 cm^{-1}. δ_H (400 MHz) 1.30 (3H, s, 3-Me), 2.45 (1H, dd, *J* 15.8, 2.2 Hz, H 2), 2.55 (1H, dd, *J* 15.8, 2.2 Hz, H 2), 2.88 (1H, d, *J* 13.6 Hz, H 4), 2.92 (1H, d, *J* 13.6 Hz, H 4), 3.74 and 3.78 (each 3H, s, OMe), 6.69–6.83 (3H, m, ArH), 9.83 (1H, t, *J* 2.2 Hz, H 1). δ_C (100 MHz) 27.8, 42.9, 53.9, 55.6, 55.8, 72.4, 111.6, 112.3, 118.7, 126.4, 151.5, 153.5, 203.2. *m/z* 238 (M^+, 4.5%), 194 (49), 152 (32), 151 (100), 137 (29), 121 (77), 91 (45), 77 (27), 43 (52), 28 (38).

(ii) *Pyridinium dichromate*. To a solution of the alcohol (±)-(22) (100 mg, 0.417 mmol) in dichloromethane (2 ml) was added successively pyridinium dichromate (233 mg, 0.619 mmol), freshly activated powdered 3 Å molecular sieves and glacial acetic acid (55 μl, 1.0 mmol). The solution was stirred for 1.5 h at room temperature, diluted with ether (5 ml) and filtered through a pad of Celite©. The filtrate was concentrated under reduced pressure and and the residue was purified by flash pad chromatography using a gradient of light petroleum/ether as eluent. Distillation gave the aldehyde (±)-(10) (37.0 mg, 37%) that was, with the exception of specific rotation, identical with the material described above. A less polar fraction gave 2,5-dimethoxybenzaldehyde (24) (11.2 mg, 16%), m.p. 49–51°C, which was identical to authentic material.

(iii) *Tetrapropylammonium perruthenate*. A mixture of the alcohol (±)-(22) (143 mg, 0.596 mmol), *N*-methylmorpholine *N*-oxide (104 mg, 0.888 mmol) and powdered 3 Å molecular sieves (30 mg) in dichloromethane (2 ml) was stirred at room temperature for 10 min. Tetrapropylammonium perruthenate (12 mg, 0.034 mmol) was added and the reaction mixture was stirred for 18 h at room temperature. The mixture was diluted with ethyl acetate (20 ml) and filtered through a pad of silica gel. The solvent was evaporated to dryness and the residue was purified by flash pad chromatography using a gradient solvent system of light petroleum/ether to give the aldehyde (±)-(10) (40.0 mg, 28%) together with unchanged (±)-(22) (15.7 mg, 11%) and 1-(2′,5′-dimethoxyphenyl)propan-2-one (25) (12.7 mg, 12%), b.p. 110–120°C/0.1 mmHg (lit.[33] b.p. 100°C/0.07 mmHg). δ_H (300 MHz) 2.13 (3H, s, 3-Me), 3.63 (2H, s, $H_2$1), 3.72 and 3.73 (each 3H, s, OMe), 6.70–6.80 (3H, m, ArH).

(iv) *Swern oxidation*. A solution of dimethyl sulfoxide (0.60 ml, 8.5 mmol) in dichloromethane (2 ml) was added dropwise to a solution of oxalyl chloride (0.37 ml, 4.2 mmol) in dichloromethane (8 ml) at –50 to –60°C. The reaction mixture was stirred for 2 min and a solution of (±)-(22) (880 mg, 3.67 mmol) in dichloromethane (2 ml) was added over 5 min. The mixture was stirred for a further 20 min and triethylamine (2.6 ml, 19 mmol) was added. After 5 min, the reaction mixture was allowed to warm to room temperature. Water (15 ml) was added and the products were extracted into dichloromethane (2×15 ml). The combined extract was washed with brine (30 ml), hydrochloric acid (1 M, 3×30 ml), water (2×30 ml), and dried. The solvent was evaporated and the residue was purified by flash pad chromatography using a gradient of light petroleum/ether. Distillation gave the aldehyde (±)-(10) (438 mg, 50%) that was, with the exception of specific rotation, identical with the material described above.

(1S,3S)-5,8-Dimethoxy-3-methyl-1,2,3,4-tetrahydronaphthalene-1,3-diol (23)

A solution of tin(IV) chloride (350 μl, 2.99 mmol) in dichloromethane was added slowly to a solution of the aldehyde (10) (175 mg, 0.734 mmol) in dichloromethane (8 ml) at –78°C. The solution was allowed to warm to –25°C over 3.5 h before triethylamine (350 μl, 2.51 mmol) was added and the solution was diluted with dichloromethane (50 ml). The solution was washed with cold sodium hydroxide (1 M, 3×30 ml), water (2×30 ml), dried and evaporated. The residue was crystallized from ethyl acetate to give the (1*S*,3*S*)-tetrahydronaphthalene (23) as colourless *prisms* (147 mg, 84%), m.p. 167–169°C {(±)-(23) m.p. 163–165°C} (Found: C, 65.6; H, 7.9. $C_{13}H_{18}O_4$ requires C, 65.5; H, 7.6%). $[\alpha]_D$ –6.8 (*c*, 2.6) {(1*R*,3*R*) *ent*-(23) $[\alpha]_D$ +7.1 (*c*, 2.6)}. ν_{max} 3265, 2962, 1480, 1256 cm^{-1}. δ_H (400 MHz) 1.42 (3H, s, 3-Me), 1.65 (1H, br s, OH), 1.85 (1H, dd, *J* 14.5, 5.0 Hz, H 2), 2.26 (1H, ddd, *J* 14.5, 2.2, 2.2 Hz, H 2), 2.46 (1H, d, *J* 17.7 Hz, H 4), 3.07 (1H, dd, *J* 17.7, 2.2 Hz, H 4), 3.26 (1H, br s, OH), 3.79 and 3.85 (each 3H, s, OMe), 5.17 (1H, m, H 1), 6.71–6.81 (2H, m, ArH). δ_C, (100 MHz) 30.1, 37.7, 40.4, 55.6, 55.7, 63.9, 68.1, 107.4, 109.4, 124.8, 126.3, 151.5, 151.7. *m/z* 238 (M^+, 3.3%), 202 (37), 187 (100), 159 (26), 18 (34).

(1S,3S)-1,3-Dihydroxy-3-methyl-1,2,3,4-tetrahydro-5,8-naphthoquinone (9)

A solution of ammonium cerium(IV) nitrate (341 mg, 0.622 mmol) in water (6 ml) was added over 5 min to a stirred solution of the quinol dimethyl ether (23) (74 mg, 0.31 mmol) in acetonitrile (6 ml). The mixture was stirred at room temperature for 5 min and then diluted with water (30 ml). The products were extracted into dichloromethane (5×20 ml), dried and evaporated to give the (1*S*,3*S*)-naphthoquinone (9) (65 mg, 100%) as a yellow *gum* (Found: M^+, 208.0737. $C_{11}H_{12}O_4$ requires M^+, 208.0736). $[\alpha]_D$ –63 (*c*, 0.81 in EtOH) {(1*R*,3*R*) *ent*-(9) $[\alpha]_D$ +62 (*c*, 0.80 in EtOH)}. δ_H (400 MHz) 1.41 (3H, s, 3-Me), 1.77 (1H, dd, *J* 14.7, 5.1 Hz, H 2), 2.24 (1H, ddd, *J* 14.7, 2.2, 2.2 Hz, H 2), 2.30 (1H, dd, *J* 19.8, 1.5 Hz, H 4), 2.86 (1H, dd, *J* 19.8, 2.2 Hz, H 4), 3.07 (1H, m, OH), 4.91 (1H, m, H 1), 6.79 (2H, m, ArH). δ_C (100 MHz) 29.9, 37.0, 40.0, 62.2, 68.2, 136.3, 136.6, 139.5, 140.3, 187.2, 187.6. *m/z* 208 (M^+, 27%), 205 (24), 190 (70), 189 (45), 180 (30), 177 (90), 165 (33), 151 (46), 150 (95), 149 (21), 148 (100), 147 (50), 137 (21), 123 (24), 122 (24), 91 (31) 77 (22), 65 (26), 53 (20).

(1S,3S)-Austrocortilutein (1)

A solution of 1,3-dimethoxy-1-trimethylsilyloxybuta-1,3-diene (8)[6] (40 mg, 0.20 mmol) and the (1*S*,3*S*)-naphthoquinone (9) (34.1 mg, 0.164 mmol) in benzene (5 ml) was stirred at room temperature for 9 h. Water (7 ml) was added and the mixture stirred vigourously in an open flask for 12 h. The mixture was diluted with dichloromethane (30 ml) and washed with water (2×15 ml), dried and evaporated to dryness. Preparative thin-layer chromatography with toluene/ethyl formate/formic acid (50 : 49 : 1) gave a mixture (20 mg, 40%) of (1*S*,3*S*)-austrocortilutein (1) and its regioisomer (31) in a 4 : 1 ratio by ^{1}H n.m.r. spectroscopy. Fractional crystallization from chloroform gave (1*S*,3*S*)-austrocortilutein (1) (11.1 mg, 22%) as orange-yellow needles, m.p. 182–185°C (lit.[1] 183–185°C), $[\alpha]_D$ +55 (*c*, 0.10), lit.[1] $[\alpha]_D$ +52 (*c*, 0.095) {(1*R*,3*R*)-austrocortilutein (5) $[\alpha]_D$ –63 (*c*, 0.24 in EtOH), lit.[25] $[\alpha]_D$ –61 (*c*, 0.24 in EtOH)} (Found: M^+, 304.0955. Calc. for $C_{16}H_{16}O_6$: M^+, 304.0946). λ_{max} 221 (log ϵ 4.62), 270 (4.17), 283sh (3.93), 427 nm (3.64). ν_{max} 3392, 2975, 1666, 1639, 1605, 1384, 1298, 1267, 1205, 1147 cm^{-1}. δ_H (1), see Table 1; δ_H (5), see Table 3. *m/z* 304 (M^+, 42%), 286 (77), 271 (24), 269 (21), 268 (88), 262 (33), 247 (24), 246 (61), 245 (24), 244 (100), 243 (56), 219 (34), 218 (59), 151 (36), 115 (22).

The tetrahydronaphthalene (31) was not obtained in spectroscopically pure form; consequently, the ^{1}H n.m.r data that follow were deduced from the spectrum of a mixture of (1) and (31) by subtraction of the signals from the former. (1*S*,3*S*)-1,3,5-Trihydroxy-7-methoxy-3-methyl-1,2,3,4-tetrahydroanthracene-9,10-dione (31) δ_H (300 MHz) 1.45 (3H, s, 3-Me), 1.82 (1H, dd, *J* 14.7, 5.1 Hz, H_{ax}2), 2.32 (1H, ddd, *J* 14.7, 1.8, 1.8 Hz, H_{eq}2), 2.41 (1H, dd, *J* 19.8, 1.5 Hz, H_{ax}4), 3.05 (1H, dd, *J* 19.8, 1.8 Hz, H_{eq}4), 3.08 (1H, m, 3-OH), 3.51 (1H, m, OH), 3.91 (3H, s, 7-OMe), 5.08 (1H, m, H 1), 6.64 (1H, d, *J* 2.4 Hz, H 6), 7.17 (1H, d, *J* 2.4 Hz, H 8), 12.24 (1H, s, 5-OH).

(1S,3S)-Austrocortirubin 5-O-Methyl Ether (34)

A solution of 1,3,4-trimethoxy-1-trimethylsilyloxybuta-1,3-diene (33)[22] (68.0 mg, 0.278 mmol) and the (1*S*,3*S*)-naphthoquinone (9) (33.2 mg, 0.160 mmol) in benzene (5 ml) was stirred at room temperature for 18 h. Water (10 ml) was added and the mixture was stirred vigorously for 12 h in an open flask. The mixture was diluted with dichloromethane (50 ml) and washed with water (2×25 ml), dried and evaporated. Purification of the residue by using flash pad chromatography with toluene/ethyl formate/formic acid (50 : 49 : 1) as eluent gave a mixture (13.4 mg, 25%) of (1*S*,3*S*)-austrocortirubin 5-*O*-methyl ether (34) and its regioisomer (35) in a 4 : 1 ratio by ^{1}H n.m.r. spectroscopy. Fractional crystallization of the mixture from benzene gave the title compound (34) (7.8 mg, 15%) as pale red *needles*, m.p. 175–178°C, $[\alpha]_D$ +15.9 (*c*, 0.27) (Found: M^+, 334.1053. $C_{17}H_{18}O_7$ requires M^+, 334.1052). λ_{max} 225 (log ϵ 4.70), 275 (4.16), 454 nm (3.77). ν_{max} 3442, 1684, 1646, 1478 cm^{-1}. δ_H (300 MHz) 1.44 (3H, s, 3-Me), 1.82 (1H, dd, *J* 14.6, 5.1 Hz, H_{ax}2), 2.28 (1H, ddd, *J* 14.6, 1.8, 1.8 Hz, H_{eq}2), 2.40 (1H, dd, *J* 19.9, 1.5 Hz, H_{ax}4), 3.01 (1H, dd, *J* 19.9, 1.8 Hz, H_{eq}4), 3.86 and 3.95 (each 3H, s, OMe), 5.09 (1H, m, H 1), 6.65 (1H, s, H 7), 13.01 (1H, s, 8-OH). *m/z* 334 (M^+, 100%), 316 (21), 301 (75), 283 (23), 273 (46), 259 (53), 83 (54).

(1S,3S)-Austrocortirubin (2)

A solution of boron trichloride in dichloromethane (1 M, 280 μl, 0.28 mmol) was added dropwise to a solution of the methyl ether (34) (9.4 mg, 0.028 mmol) in dichloromethane (25 ml) at –78°C. The mixture was stirred at –78°C for 4 h and methanol (8 ml) was added. The mixture was diluted with dichloromethane (50 ml) and the solution was washed with water (3×25 ml), dried and evaporated to dryness. Flash pad chromatography with toluene/ethyl formate/formic acid (50 : 49 : 1) gave a red zone (6.8 mg, 80%) that was crystallized from benzene to give (1*S*,3*S*)-austrocortirubin (2) as bright red needles, m.p. 193–195°C (lit.[1] m.p. 193–195°C) $[\alpha]_D$ +34 (*c*, 0.54) {lit.[1] $[\alpha]_D$ +34 (*c*, 0.543)} (Found: M^+, 320.0886. Calc. for $C_{17}H_{18}O_7$: M^+, 320.0895). λ_{max} 229 (log ϵ 4.56), 304 (3.96), 475 (3.83), 506 (3.89), 542 nm (3.71). ν_{max}

3445, 1602, 1409, 1256 cm^{-1}. δ_H see Table 2. *m/z* 320 (M^+, 92%), 303 (16), 302 (72), 287 (38), 284 (42), 278 (21), 260 (49), 259 (50), 245 (30), 244 (100), 242 (22).

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