Asymmetric Synthesis of 3-Methyl-2-phenyl-1,4-benzodioxanes. Absolute Configuration of the Neolignans Eusiderin and Eusiderin C and D

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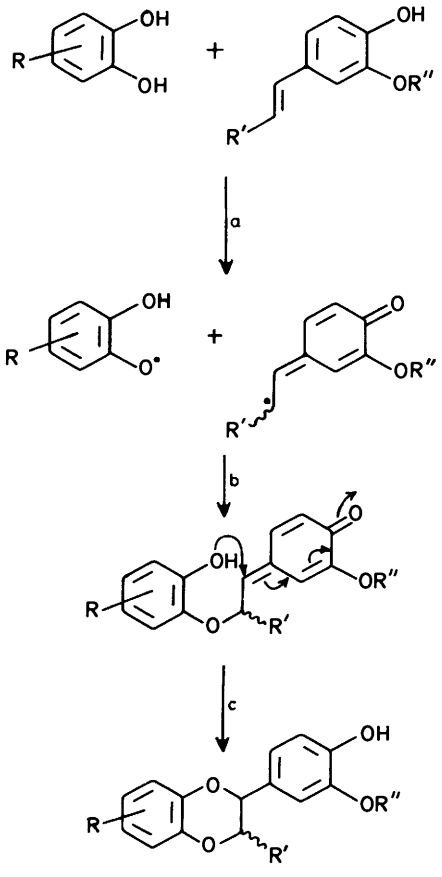
The asymmetric synthesis of 2*S*,3*S*- and 2*R*,3*S*-3-methyl-2-phenyl-1,4-benzodioxane from (−)-ephedrine is reported. Comparison of the c.d. curves of these compounds with those of the natural neolignans eusiderin and eusiderin C allows the assignment of 2*R*,3*R* configuration to eusiderin and of 2*R*,3*S* configuration to eusiderin C and eusiderin D.

Several of the many natural neolignans[1] or lignoids contain a 1,4-benzodioxane ring. Despite the simplicity of the structure, which is derived by phenol coupling of two C_6C_3 units, the correct structural elucidation of these compounds has met with considerable difficulties. This is due to the biosynthetic process, which, according to a widely accepted hypothesis[2] and some experimental evidence,[3] consists of a phenol oxidation induced by peroxidase or a similar enzyme (step a), followed by O-β coupling of the phenoxy radicals (or their mesomeric forms) (step b), and ring closure of the quinone methides thus formed (step c, Scheme 1). Since b and c may not be enzymatically

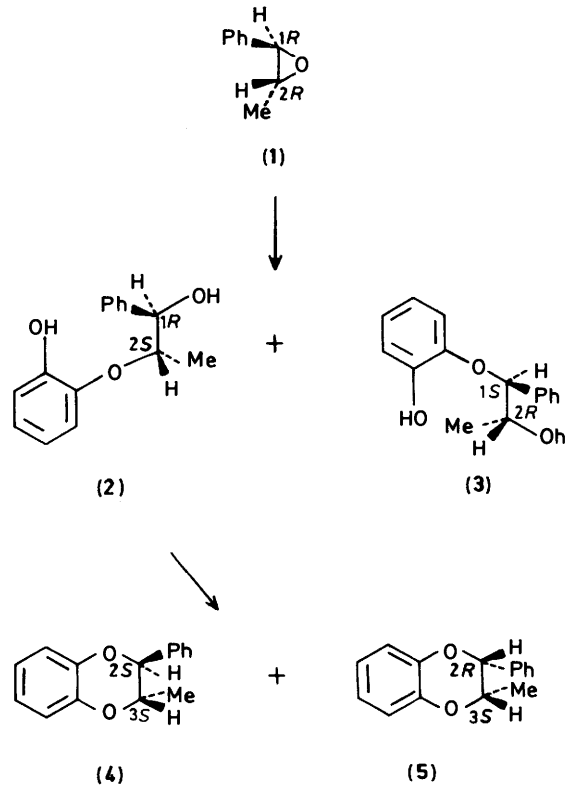


Scheme 1.

controlled, the coupling may give rise, in most cases, to mixtures of regio- and stereo-isomers.[4] The correct assignment of the structure of the regioisomers requires sophisticated interpretation of the n.m.r. spectra.[5] The relative configuration at carbons 2 and 3 is easily assigned on the basis of the 2-H,3-H coupling constants, which have characteristically different values for *cis* (*J ca.* 2 Hz) and *trans* (*J ca.* 8 Hz) isomers.[6] Most natural compounds possess a *trans* configuration, a fact that may be consistent with thermodynamic control of step c.

An unsolved problem in this area has been the assignment of the absolute configuration of those few, natural benzodioxane neolignans, which are not racemic. Again the presence of racemic mixtures in Nature would be consistent with a non-stereoselective step b. We present here a solution to this problem, *via* the asymmetric synthesis of (−)-*cis*- and (+)-*trans*-3-methyl-2-phenyl-1,4-benzodioxane, as model compounds, and comparison of their c.d. absorption curves with those of two representatives of optically active natural neolignans, eusiderin[7] and eusiderin C.[8]

In a classic paper of 1957, Witkop[9] reported the preparation of optically active 1-phenyl-1,2-epoxypropanes from ephedrines.

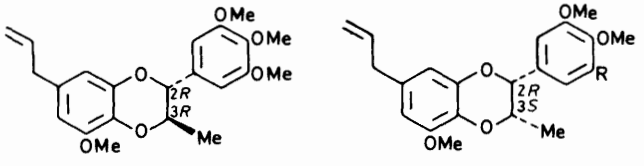


Scheme 2.

Thus, alkali treatment of (−)-ephedrine methiodide afforded (+)-1*R*,2*R*-1-phenyl-1,2-epoxypropane (**1**). Reaction of (**1**) with the sodium salt of pyrocatechol gave two products, to which structures (**2**) and (**3**) respectively were assigned on the basis of the shift of the C*H*OH proton n.m.r. signal upon acetylation. They clearly derive from the expectedly non-regioselective nucleophilic attack on the oxirane ring. Both show *erythro* configuration, as indicated by the low coupling constant (*J ca.* 4 Hz),[10] and appear of maximum optical purity, on the basis of n.m.r. experiments with lanthanide shift reagents. It follows that the expected inversion at C-2 or C-3 respectively of (**1**) has occurred, and therefore the configuration of the alcohols is 1*R*,2*S* for (**2**) and 1*S*,2*R* for (**3**). Ring closure with a strongly acid ionic exchanger in toluene of (**2**) gave a mixture of a *cis*- and a *trans*-1,4-benzodioxane, which were separated by chromatography, their purity being checked by capillary g.l.c. Their formation under these conditions requires a S_N1 reaction at the benzylic carbon, and therefore 2*S*,3*S* configuration can be assigned to (+)-*trans*-3-methyl-2-phenyl-1,4-benzodioxane (**4**), and 2*R*,3*S* *to* (−)-*cis*-3-methyl-2-phenyl-1,4-benzodioxane (**5**) (Scheme 2).

Knowledge of the absolute configuration of compounds (**4**) and (**5**) allows a determination of the stereochemistry of the natural products eusiderin (**6**) and eusiderin C (**7**) (Scheme 3). The c.d. spectra[11] of these compounds (see Figure) look quite similar (apart from the signs of the bands) and it is to be noticed that the *cis* derivatives show bands which are red shifted in comparison with the *trans* ones. Compounds (**4**) and (**5**) possess similar chromophoric systems to those of (**6**) and (**7**), the only difference being due to the presence of methoxy groups on the phenyl substituent in position 2 of (**6**) and (**7**) and the allyl and methoxy group on the benzodioxane moiety. The above close similarity between the chromophoric systems now allows a correct comparison of the c.d. curves of (**4**) and (**5**) with those of (**6**) and (**7**). The observation that the *trans* compound (**4**) shows a c.d. spectrum in the range* 250—220 nm which is, in practice, the mirror image of *trans*-eusiderin suggests that compounds (**4**) and (**6**) have opposite configuration at the chiral centre.

At the same time, compound (**5**) and *cis*-eusiderin show c.d. curves of the same sign in the above spectral region suggesting that the natural compound has the same absolute configuration (2*R*,3*S*) of the reference product. As Gottlieb[8] has assigned the same relative configuration as for eusiderin C also to eusiderin D (**8**), that of this latter is also established.



(**6**) (**7**) R = OMe (**8**) R = H

Scheme 3.

Comparison of the intensity of the c.d. absorption, although of differently substituted compounds, leads us to suppose that natural eusiderins are of high optical purity.

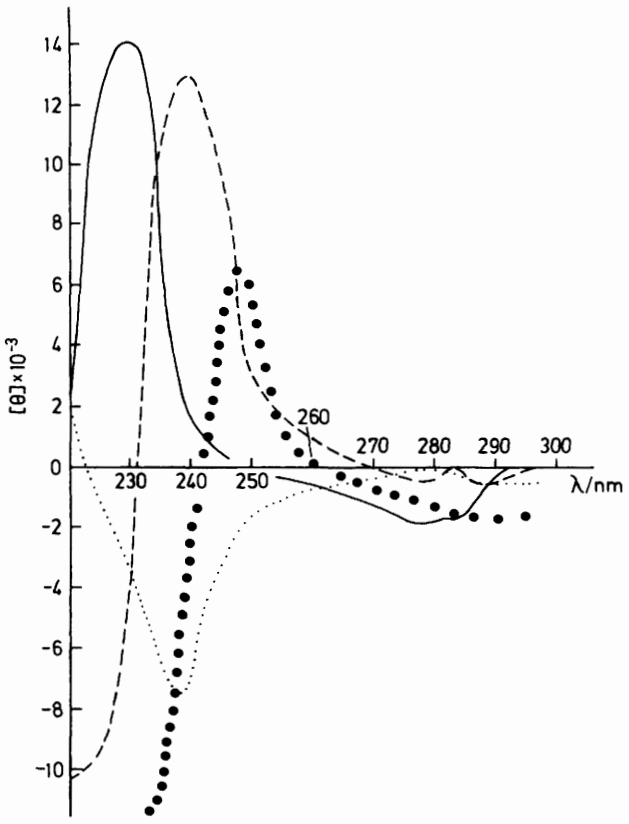


Figure. C.d. spectra of —— *trans*-(2*S*,3*S*)-3-methyl-2-phenyl-1,4-benzodioxane (**4**), – – – – *cis*-(2*R*,3*S*)-3-methyl-2-phenyl-1,4-benzodioxane (**5**), · · · · eusiderin (**6**) and * * * * eusiderin C (**7**).

Eusiderins are the only natural benzodioxane neolignans so far isolated and found to be optically active. Both *cis* and *trans* isomers occur in plants, *e.g. Virola* (Myristicaceae),[8] together with the corresponding open-chain compounds (*e.g.* surinamensin and virolin);[13] this leads us tentatively to suggest that their biosynthesis might perhaps occur *via* a different pathway from that of Scheme 1, *i.e.* from a pyrocatechol unit and a C_6C_3 unit with an oxirane function (or also, as suggested by a Referee, by Scheme 1, but in a stepwise fashion, with reductive trapping of the quinone methide intermediate).

Experimental

M.p.s are uncorrected. Mass spectra were obtained with a Finnigan 4021 mass spectrometer equipped with INCOS data system. ^{1}H N.m.r. spectra were measured at 80 MHz with a Bruker WP80SY spectrometer; chemical shifts are in δ (p.p.m.) from $SiMe_4$ as internal standard. Column chromatography was performed by the 'flash chromatography' method on silica gel Merck 60. Circular dichroism spectra were measured with a JASCO 500A spectropolarimeter, with N_2 flux of 4.5 ml min^{-1} at 3 atm.

(1R,2S)-2-(2-*Hydroxyphenoxy*)-1-*phenylpropan*-1-*ol* (**2**) *and* (1S,2R)-1-(2-*Hydroxyphenoxy*)-1-*phenylpropan*-2-*ol* (**3**).—Pyrocatechol (0.9 g, 8.2 mmol) in DMF (3 ml) was dropped in a slurry of NaH (80% in paraffin oil; 0.40 g) in DMF (2 ml) under nitrogen, to give a grey suspension of the sodium salt. A solution of the epoxide[9] (**1**) {$[\alpha]_D$ +45.9° (*c* 0.63 in $CHCl_3$) [lit.,[9] + 48.2° (*c* 1.1)]} in DMF (2 ml) was then dropped in, and the

* The long wavelength band, 260—300 nm, cannot be considered as significant for the present purpose. In fact, this absorption is allied to the forbidden ^1L_b transition of substituted phenyl chromophores and, as it has been shown[12] in the case of simple *para* substituted phenylethylamines, the c.d. spectra do not show any correlation between absolute configuration and sign of the Cotton effect.

mixture refluxed for 5 h; it was then cooled, diluted with water (20 ml), and extracted with AcOEt (3 × 20 ml). Chromatography of the extract with hexane–AcOEt (7:3) gave (**2**) (0.33 g, 16%) and (**3**) (0.62 g, 31%). Compound (**2**) has b.p. 115—120 °C/0.1 Torr (in Kugelrohr), $[\alpha]_D$ +3.44° (*c* 0.174 in $CHCl_3$) (Found: C, 74.0; H, 7.0. Calc. for $C_{15}H_{16}O_3$: C, 73.8; H, 6.6%); $\delta_H(CDCl_3)$ 1.21 (3 H, d, *J* 5.5, Me), 4.40 (1 H, dq, 2-H), 4.91 (1 H, d, *J* 4, 1-H), 6.7—7.0 (4 H, ArH), and 7.2—7.5 (5 H, ArH); *m/z* 244 (M^+, 8%), 226 (6), 138 (7), 137 (32), 135 (10), 117 (9), 110 (100), and 77 (22); c.d. (*c* 0.087 in $CHCl_3$) $[\theta]_{230}$ +15 700, $[\theta]_{251}$ +1 150, $[\theta]_{256}$ +1 420, $[\theta]_{261}$ +2 180, $[\theta]_{264}$ +1 990, $[\theta]_{268}$ +2 840, $[\theta]_{272}$ +2 460, $[\theta]_{276}$ + 2 800, $[\theta]_{290}$ +336.

Compound (**3**) has b.p. 105—110 °C/0.15 Torr (Kugelrohr); $[\alpha]_D$ −11.7° (*c* 0.35 in MeOH); $\delta_H(CDCl_3)$ 1.23 (3 H, d, *J* 6, Me), 4.20 (dq, 2-H), 5.00 (1 H, d, *J* 4, 1-H), 6.6—7.0 (4 H, ArH), and 7.2—7.5 (5 H, ArH); *m/z* 244 (M^+, 0.5%), 199 (3), 153 (2), 135 (19), 117 (14), 110 (100), 91 (30), and 77 (14). Acetylation with Ac_2O and pyridine of (**2**) gave the *diacetate* of (**2**), $\delta_H(CDCl_3)$ 1.25 (3 H, d, Me), 2.11 (3 H, s, MeCO), 2.23 (3 H, s, MeCO), 4.68 (1 H, dq, 2-H), 5.95 (1 H, d, *J* 4, 1-H, 6.8—7.2 (4 H), and 7.2—7.5 (5 H). A similar reaction with (**3**) gave diacetate, δ_H 1.26 (3 H, d, Me), 1.98 (3 H, s, MeCO), 2.31 (3 H, s, MeCO), 5.0—5.4 (1-H and 2-H), and 6.5—7.2 (4 H), 7.2—7.5 (5 H).

LIS Experiments on Compound (**2**).—A solution of $[Eu(hfc)_3]$ (0.062 mmol) in $CDCl_3$ was added stepwise to solutions of (+)-(**2**) (25 mg) or (±)-(**2**) (prepared by 3-chloroperbenzoic acid oxidation of propenylbenzene) in $CDCl_3$ (1 ml). Addition of 0.4 mol equiv. of the reagent to (±)-(**2**) gave rise to two doublets for the Me group (Δδ 0.45) in the ^1H n.m.r. spectrum; no such effect was observed for (+)-(**2**).

(2S,3S)-3-*Methyl*-2-*phenyl*-1,4-*benzodioxane* (**4**) *and* (2R,3S)-3-*Methyl*-2-*phenyl*-1,4-*benzodioxane* (**5**).—Compound (**2**) (350 mg) was refluxed for 1.5 h in toluene (3 ml) with Amberlyst 15 (50 mg). The solution was filtered, dried, and evaporated to give a residue containing (**4**) and (**5**) (6:4 ratio, by g.l.c.), which was chromatographed on silica gel with light petroleum the fractions being monitored by capillary g.l.c. (SP-2100, 30 m, carrier He 4.5 ml, split 100 ml, septum 10, *t* 170 °C). Only the fractions containing >97% of a single isomer were collected. Thus 25 mg of (+)-(**4**) and 26 mg of (−)-(**5**) were obtained.

Compound (**4**) is an oil (Found: C, 80.0; H, 6.6. $C_{15}H_{14}O_2$ requires C, 79.6; H, 6.2%), $\lambda_{max.}$ (MeOH) 204 (ε 11 220 dm^3 mol^{-1} cm^{-1}), 277 (1 095), and 283 (850); $[\alpha]_D$ +3.03° (*c* 0.066 in MeOH); c.d. (*c* 0.33 g l^{-1} in MeOH) $[\theta]_{230.5}$ +14 250, $[\theta]_{250}$ 0, $[\theta]_{278}$ −1 900, $[\theta]_{283.5}$ −1 780; δ_H 1.19 (3 H, d, *J* 6, Me), 4.13 (1 H, dq, 3-H), 4.63 (1 H, d, *J* 7, 2-H, and 6.88 (4 H), 7.38 (5 H); *m/z* 226 (M^+, 34%), 183 (4), 135 (46), 121 (27), 118 (100), 117 (90), 115 (33), 110 (9), and 91 (39). Compound (**5**) (Found: C, 79.3; H, 6.1; $C_{15}H_{14}O_2$ requires C, 79.6; H, 6.2%) has $\lambda_{max.}$(MeOH) 204 (ε 39 800 dm^3 mol^{-1} cm^{-1}), 278 (3 630), and 284 (3 220); $[\alpha]_D$ −65.5° (*c* 0.084 in MeOH); c.d. (*c* 0.21 g l^{-1} in MeOH) $[\theta]_{225}$ −9 040, $[\theta]_{231.5}$ 0, $[\theta]_{237.5}$ +12 900, $[\theta]_{271}$ 0, $[\theta]_{280.5}$ −430, $[\theta]_{283.5}$ 0, $[\theta]_{287.5}$ −650; δ_H 1.10 (3 H, d, *J* 6, Me), 4.53 (1 H, dq, *J* 3, 6, 3-H), 5.18 (1 H, d, *J* 3, 2-H), 6.90 (4 H), and 7.35 (5 H, s).

Eusiderin (**6**).[11]—C.d. (*c* 0.24 g l^{-1} in MeOH) $[\theta]_{212.5}$ 0, $[\theta]_{215}$ +6 750, $[\theta]_{222}$ 0, $[\theta]_{242.5}$ −750, and $[\theta]_{280}$ 0.

Eusiderin C (**7**).[11]—C.d. (*c* 0.16 g l^{-1} in MeOH) $[\theta]_{220}$ −17 600, $[\theta]_{242}$ 0, $[\theta]_{247.5}$ +6 520, $[\theta]_{260}$ 0, and $[\theta]_{290}$ −690.

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