Racemization of Phenanthrene 3,4-Oxide. Absolute Stereochemistry of *cis*- and *trans*-Phenanthrene 3,4-Dihydrodiols

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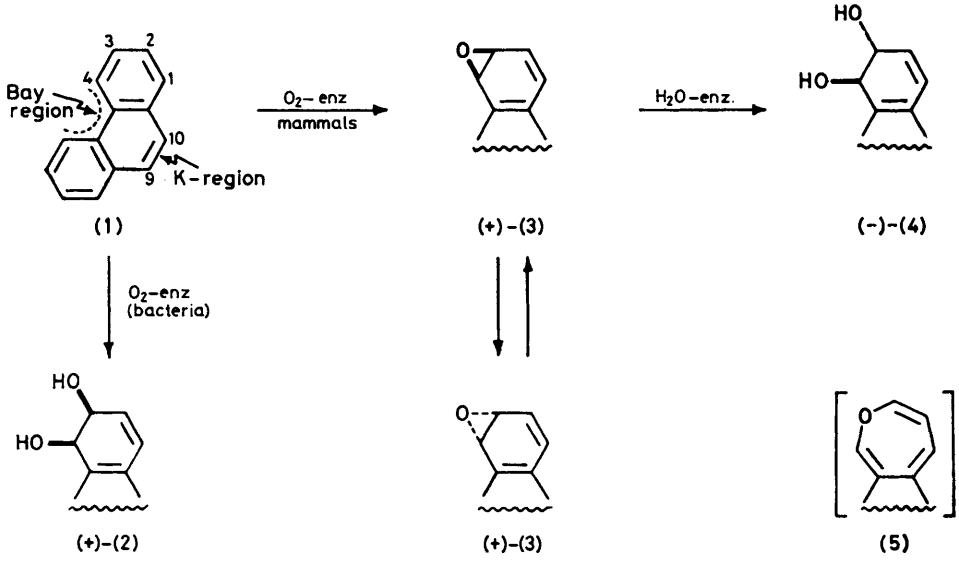
trans-3,4-Dihydroxy-1,2,3,4-tetrahydrophenanthrene (11) and *cis*-3,4-dihydroxy-1,2,3,4-tetrahydrophenanthrene (12) have been prepared in optically pure form *via*: (i) chromatographic separation of the *trans*-3-bromo-4-menthyloxyacetoxy-1,2,3,4-tetrahydrophenanthrene diastereoisomers (7a),(7b), (ii) conversion of (7a) into the optically pure (+)-tetrahydro-3,4-epoxide (8), (iii) acid-catalysed hydrolysis of (+)-(8) by attack at C-4 to yield (+)-*trans*-(11) and (−)-*cis*-(12). Several lines of evidence, including spectral methods and chemical transformation to compounds of known absolute stereochemistry, have been used to assign absolute stereochemistry to all chiral compounds described in the present study. The availability of optically pure diols (11) and (12) has allowed the absolute stereochemistry of the *trans*- and *cis*-3,4-dihydrodiol metabolites of phenanthrene (4) and (2) to be determined as (−)-(3*R*,4*R*) and (+)-(3*S*,4*R*) respectively. Phenanthrene 3,4-oxide, an initial mammalian metabolite of phenanthrene prepared from optically pure precursors, was optically active but racemized spontaneously at ambient temperature.

THE metabolism of phenanthrene in mammalian and bacterial systems has been the subject of several previous reports.[1-5] Phenanthrene is of particular interest in view of its widespread distribution in the environment and since it is the simplest member of the polycyclic aromatic hydrocarbon (PAH) series to have a ' bay-region ' (Scheme 1). The latter is an essential structural feature in the ' Bay-Region Theory ' [6] which has been used to link mutagenic and carcinogenic activity with the structure of PAH metabolites.

Phenanthrene is transformed into *trans*-9,10-(major), *trans*-1,2-(minor) and *trans*-3,4-(minor) dihydrodiol metabolites *via* mono-oxygenase catalysed addition of an oxygen atom to form arene oxides, followed by epoxide hydrolase-catalysed hydration in mammalian liver systems.[1,2,4,5] In bacterial cultures, phenanthrene is converted into *cis*-3,4-(major) and *cis*-1,2-(minor) dihydrodiols through the action of dioxygenase enzymes and molecular oxygen.[3,4] The absolute stereochemistry of compounds (2), (3), and (4), which are the metabolites of phenanthrene resulting from enzyme-catalysed attack at the 3,4-bond,[4,5] is unequivocally assigned in the present report (Schemes 1 and 2).

trans-3-Bromo-4-hydroxy-1,2,3,4-tetrahydrophenanthrene (6) [7,8] was esterified using (−)-menthyloxyacetyl chloride to yield a mixture of the *trans*-3-bromo-4-menthyloxyacetoxy-1,2,3,4-tetrahydrophenanthrene diastereoisomers (7a) and (7b). A large scale (*ca.* 10 g) partial separation of this mixture was achieved initially by short-column chromatography which gave a range of optically active fractions (maximum diastereoisomeric purity *ca.* 70—75%).[9] However, a more efficient



SCHEME 1

resolution of diastereoisomers on a smaller scale (*ca.* 2 g) was accomplished using preparative high-pressure liquid chromatography (h.p.l.c.). The latter method yielded fractions with >98% diastereoisomeric purity from analytical h.p.l.c. (Figure 1). The chromato-

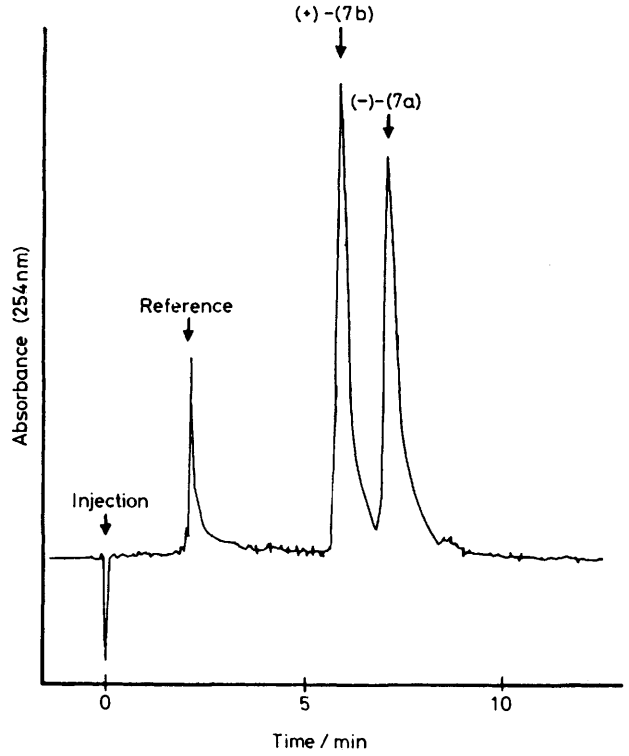


FIGURE 1 Analytical h.p.l.c. separation of compounds (7a) and (7b) [Zorbax Sil, cyclohexane–ether (97 : 3)]

graphic separation methods used for (7a) and (7b) have also proved successful for the corresponding bromo-esters in the naphthalene,[10] anthracene,[10] benz[*a*]-anthracene (B[*a*]A),[11] and benzo[*a*]pyrene (B[*a*]P)[12] series. The syntheses of compounds (6), (9a), (9b), (13a), (13b), and (3) in racemic form have previously been reported[8] and most of the interconversion steps (a—i in Scheme 2) have been used for the corresponding chiral compounds in other members of the PAH series.[10-12]

The absolute stereochemistry of the chiral compounds in Schemes 1 and 2 was determined by several methods. (i) A comparative analysis of absolute stereochemistry of the diastereoisomers (7a) and (7b) with analogues in the naphthalene,[10] anthracene,[10] B[*a*]A,[11] and B[*a*]P[12] series was made. Thus, previously it was noted that the diastereoisomer with a shorter retention time on silica-gel chromatography (less polar), with a large (>100°) negative $[\alpha]_D$ value, and with the n.m.r. signal for the exocyclic methylene protons (H_A,H_B) existing as a singlet (220 MHz, C_6D_6), had [*R*,*R*] stereochemistry. The data obtained for (7a) and (7b) was as follows: (7a): less polar, $k = 1.7$, $[\alpha]_D$ −174°, H_A,H_B 4.12δ (2 H, br s *); (7b): more polar, $k = 2.3$, $[\alpha]_D$ +58°, H_A 3.75δ, H_B 3.96δ, J_{AB} 16.3 Hz (2 H, AB quartet). On this evidence a tentative assignment of stereochemistry for (−)-(7a) is [3*R*, 4*R*].

(ii) The absolute stereochemistry of a sample of alcohol (14) ($[\alpha]_D$ −28°, *ca.* 57% optical purity) was assigned by application of the Exciton Chirality Rule.[13-16] Thus the circular dichroism (c.d.) spectrum for the benzoate ester of (−)-(14) was obtained in 10% dioxan–methanol (Figure 2). Both the 1,2,3,4-tetrahydrophenanthrene and benzoate chromophores have strong π→π* transitions at 239 nm (*ca.* 100 000; ^1A-^1B_b band[17]) and 228 nm (*ca.* 12 000; intramolecular charge-transfer band[18]) respectively. A pair of Cotton effects $\Delta\varepsilon_{232}$ + 104 and $\Delta\varepsilon_{222}$ −77 was centred at 227 nm. Since the longest wavelength first Cotton effect (232 nm) is positive, an examination of the spatial relationship between the electric transition dipole-moment vectors of the

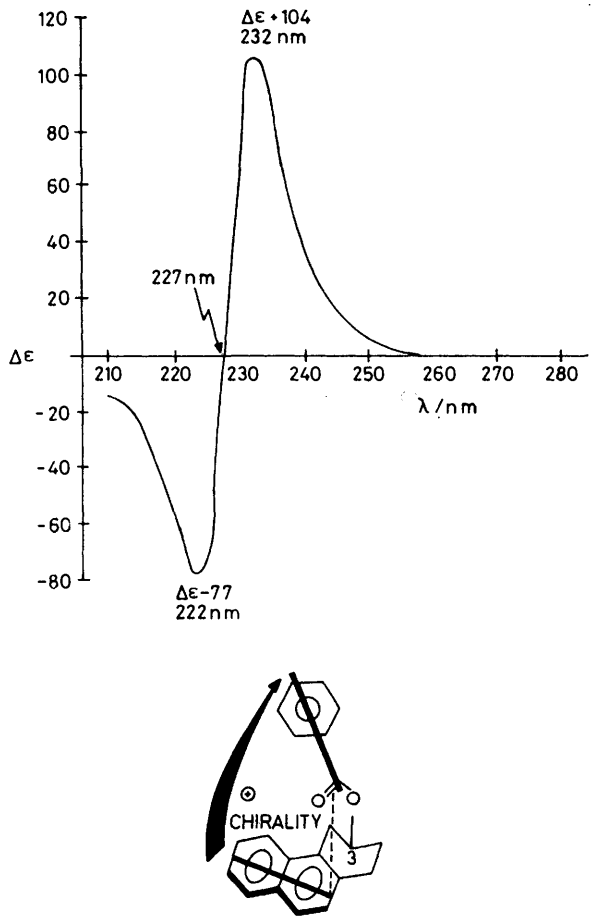
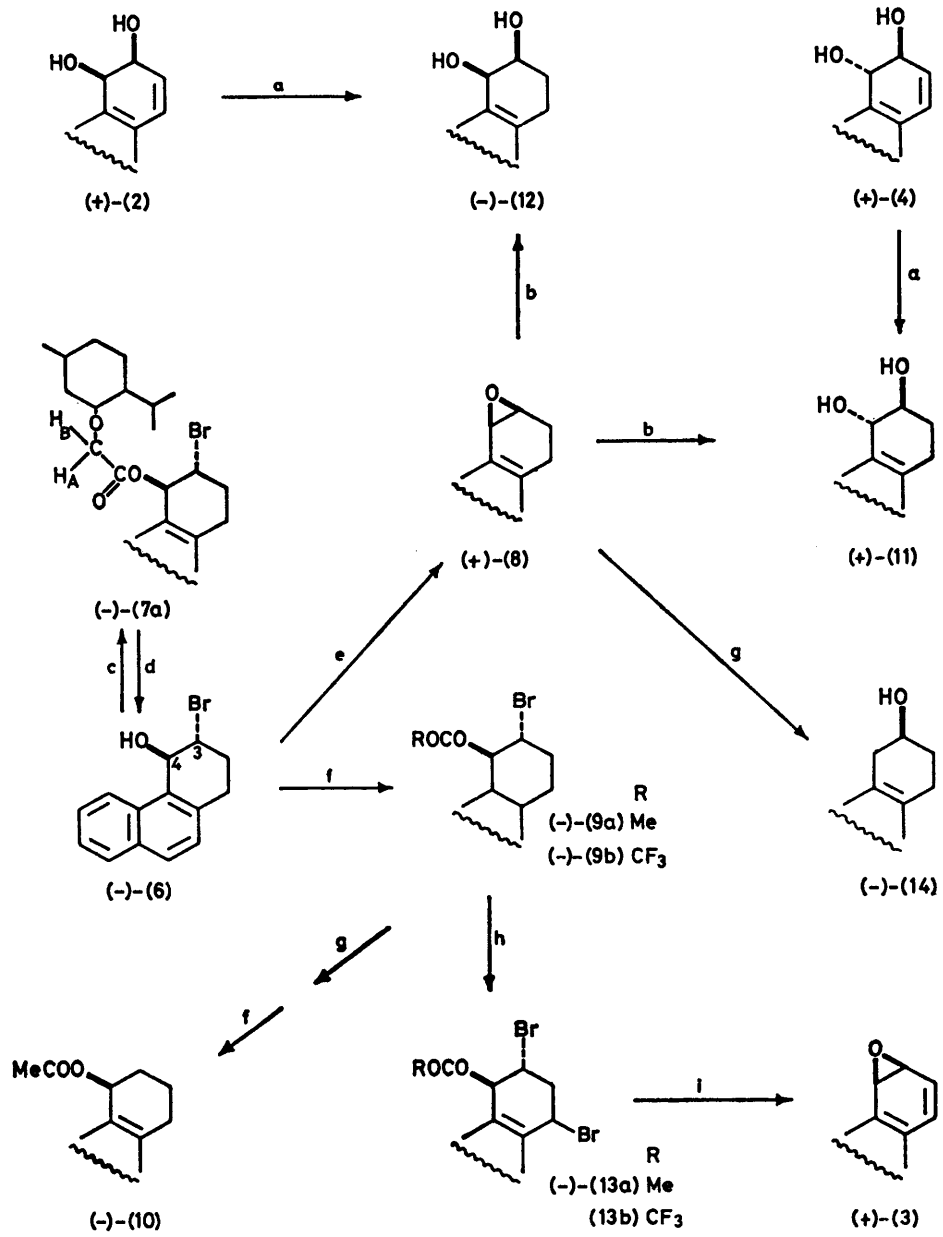


FIGURE 2 C.d. spectrum of (−)-(3*S*)-benzoyloxy-1,2,3,4-tetrahydrophenanthrene in MeOH–dioxan (9 : 1) and the configuration of the electric transition dipoles of the chromophores.

chromophores (assuming that a benzoate group in an equatorial conformation was present in accordance with the n.m.r. spectrum), as required in the Exciton Chirality Rule, is indicative of a right-handed screw configuration and thus of [3*S*] stereochemistry for the alcohol (−)-(14).

* Evidence of the signal beginning to show AB quartet characteristics was present at 220 MHz.



SCHEME 2 a, H_2/Pt–THF; b, H_2O–THF(pH 3); c, menthyloxyacetyl chloride–pyridine; d, diborane–THF; e, NaOH–THF; f, acetyl chloride–pyridine or trifluoroacetic anhydride–pyridine; g, $LiAlH_4$; h, *N*-bromosuccinimide; i, NaOMe

(iii) After publication of the initial report [9] on the absolute stereochemistry of compounds (7) and (14) and the stereochemically related compounds in Scheme 2 [based mainly upon methods (i) and (ii)], the absolute stereochemistry of (—)-(10) was independently found to be (4*S*).[18] The latter study made use of exhaustive ozonolysis to yield α-acetoxyadipic acid and α-acetoxyglutaric acids of known configuration.[18]

(iv) Mild acid-catalysed hydrolysis of (+)-(8) at C-4 (THF–water, pH 3, room temperature, 18 h) yielded the *trans*-diol (+)-(11) as a major product and the *cis*-diol (—)-(12) as a minor component. The mechanism for acid-catalysed hydrolysis of the epoxide (8) has been shown to involve carbonium ion formation at the benzylic position.[19] In an earlier study the configuration of (—)-(12) had tentatively been assigned as (3*S*, 4*R*) by an independent c.d. method.[4]

All four methods lead to a concurrent unequivocal assignment of absolute stereochemistry of the chiral molecules listed in the Table and Scheme 2. The *trans*-dihydrodiol (—)-(4) which was isolated from the metabolism of phenanthrene by mammalian liver microsomes has been hydrogenated to yield (—)-(11),[5] and thus it is established that the metabolically preferred (*ca.* 97%) enantiomer of (4), has (—)-(3*R*, 4*R*) stereochemistry as indicated in Scheme 1. Similarly the

TABLE 1

Optical rotations, optical yields, and absolute configurations of compounds (3), (6)—(13)

Compound	Optical rotation $[\alpha]_D$ (°)	Optical purity (%)	Absolute configuration
(6)	−68	100	(3*R*, 4*R*)
(7a)	−174	100	(3*R*, 4*R*)
(8)	+156	100	(3*S*, 4*R*)
(9a)	−70	70	(3*R*, 4*R*)
(9b)	−156	100	(3*R*, 4*R*)
(10)	−106	83	(4*S*)
(11)	+25 [a]	100	(3*S*, 4*S*)
(12)	−22 [a]	100	(3*S*, 4*R*)
(13a)	−30	20	(3*R*, 4*R*)
(3)	+4 ⟶ 0	[b]	(3*S*, 4*R*)
(14)	−49	100	(3*S*)

[a] Dioxan solvent. [b] Spontaneous racemization occurred.

TABLE 2

Observed optical rotations of arene oxide (3) derived from (9a) and (9b)

Compound (9a) $[\alpha]_D$ (°)	Compound (3) $[\alpha]_D$ (°)
−50	0 [a]
−156 [b]	0 [c]
−20	+4 ⟶ <1 [d,e]
+26	−20 ⟶ 0 [d,e]

[a] From (13a), reaction time 20 h. [b] Compound (9b). [c] From (13b), reaction time 20 h. [d] From (13a), reaction time 6 h. [e] Spontaneous racemization occurred.

bacterial *cis*-3,4-dihydrodiol (2) [4] must have (+)-(3*S*, 4*R*) absolute stereochemistry.

Initial attempts to prepare the chiral arene oxide (3) from bromoesters (13a) or (13b) of high enantiomeric purity (60—100%) by the literature method (NaOMe, 0—2 °C, 20 h) [8] consistently yielded a racemic sample of (3) as determined by the zero optical rotation recorded (365—589 nm) or the absence of Cotton effects in the c.d. range (220—450 nm, THF). This result was unexpected since the corresponding 1,2-arene oxides of naphthalene [10] and anthracene [10] had been characterized by both large $[\alpha]_D$ values (± 150—200°) and configurational stability, *i.e.* no measurable decrease of $[\alpha]_D$ with time, during an extended period of observation (*ca.* 24 h) under ambient conditions. In order to exclude the remote possibility that arene oxide (3) was among the small category of chiral molecules which show zero $[\alpha]_D$ values and zero c.d. effects at enantiomeric homogeneity, direct evidence for the racemization process was sought. Careful t.l.c. analysis of the reaction (13a)→(3) indicated that the reaction was complete within 6 h at 0—2 °C. Thus the product arene oxide (3) which was isolated within this period was then rapidly crystallized from solution, filtered, weighed, and transferred simultaneously in $CDCl_3$ solution to both a polarimeter tube and an n.m.r. tube (all maintained at 3 °C). Using a sample of (−)-(13a) derived from (−)-(7a) of relatively low (*ca.* 20%) diastereoisomeric purity, arene oxide (3) was obtained with a small but significant optical rotation $[\alpha]_{589}$ +4° ($[\alpha]_{436}$ +12°) which decreased to <1° after 10 h at ambient temperature. The n.m.r. spectra obtained simultaneously with the $[\alpha]$ value measurements gave no indication of decomposition over the period of observation (relative to a reference peak). The validity of this observation was supported by results obtained using (+)-(7b) of opposite configuration and of higher diastereoisomeric purity (*ca.* 72%) which again showed optical activity in the isolated arene oxide (3) ($[\alpha]_{589}$ −20°) and which totally racemized (without decomposition) over a period of 16 h in $CDCl_3$ at room temperature. The chemical synthesis of samples of arene oxide (3) in enantiomeric excess (from precursors of opposite sign of rotation) has thus been achieved and the absolute stereochemistry of (+)-(3) can be assigned as (3*S*, 4*R*). The present report (and the preliminary communication [9]) is thus the first example of an observed spontaneous racemization of an arene oxide.

To date no physical evidence for the formation of the polycyclic oxepin (5) from (3) is available. This does not, however, preclude the presence of a very minor proportion of (5) whose rapid equilibration with (3) could account for the racemization. A preliminary perturbational molecular orbital (PMO) study of the arene oxide–oxepin tautomerization (3) ⇌ (5) [9] supports this mechanism for racemization. A more comprehensive PMO analysis for a wide range of arene oxide–oxepins, and further experimental evidence for the racemization of chiral arene oxides, will be reported elsewhere.[20]

It is noteworthy that the (−)-(3*R*,4*R*)-*trans*-dihydrodiol metabolite of phenanthrene (4) formed by liver microsomes [5] is obtained in high enantiomeric purity (97%). As was found in the metabolism at the 7,8-bond of B[*a*]P by liver microsomes,[21] the highly enriched dihydrodiol in the phenanthrene case could also be accounted for by stereospecific attack of an oxygen atom to one stereoheterotopic face of the PAH. In the present example, however, it must, in addition, be assumed that stereospecific attack of water at the C-3 position occurs rapidly, *i.e.* before racemization of the arene oxide can occur, or that racemization is rapid and that only one arene oxide enantiomer is efficiently attacked. Enantioselectivity by epoxide hydrolase enzyme for the (+)-(3*S*, 4*R*) arene oxide (which is constantly regenerated by racemization) thus appears to be an interesting possibility. The extent to which racemization of (3) or other PAH arene oxides may occur during liver microsomal metabolism is presently unknown but clearly represents a novel aspect of metabolism of PAHs which will require further investigation.

EXPERIMENTAL

M.p.s were determined using a Reichert Kofler hot-stage apparatus. N.m.r. spectra were recorded using Bruker WH90 and Varian HR-220 instruments with $CDCl_3$ or C_6D_6 as solvent and tetramethylsilane as reference. Chemical shifts and coupling constants have previously been reported [8] for most of the racemic compounds and were identical to the optically active forms synthesised (Table 1). Specific optical rotations ($[\alpha]_D$) were recorded at 589 nm on a Perkin-Elmer 141 digital polarimeter in $CHCl_3$ (or $CDCl_3$) solution unless stated otherwise.

(−)-Menthyloxyacetic acid was obtained commercially (Aldrich) and racemic bromohydrin (6) was synthesised in six steps by the literature methods.[7,8]

(+) *and* (−)-trans-3-*Bromo*-4-*menthyloxyacetoxy*-1,2,3,4-*tetrahydrophenanthrene* (7a) *and* (7b).—Compounds (7a) and (7b) were formed in 95% yield as a diastereoisomeric mixture from bromohydrin (6) and (−)-menthyloxyacetyl chloride by the method reported previously for analogous bromo-esters.[10-12] The partial separation of (7a) and (7b) was initially carried out using short-column chromatography (Kiesel gel G type 60, Merck [10]) with light petroleum–ether (90 : 10) as eluant. Preparative h.p.l.c. separation of (7a) and (7b) was achieved using cyclohexane–ether (400 : 1) as eluant from a custom-made 1 in × 4 ft column of silica-gel (10 μ). The mixture of (7a) and (7b) (6.8 g) was applied as a series of injections (0.5—1.0 g) to the latter column yielding (−)-(7a) (1.3 g, *k* 1.7) and (+)-(7b) (0.8 g, *k* 2.3) with diastereoisomeric purity in excess of 98% according to h.p.l.c. analysis [Du Pont, 6.2 mm × 25 cm Zorbax Sil column, cyclohexane–ether (97 : 3)]. Both (−)-(7a) and (+)-(7b) were viscous oils which were generally used without further purification; b.p. 213 °C/0.3 mmHg (Found: C, 65.9; H, 7.1. $C_{26}H_{33}BrO_3$ requires C, 66.0; H, 7.0%) [(7a)/(7b) mixture], (−)-(7a) $[\alpha]_D$ −174°, (+)-(7b) $[\alpha]_D$ +58°.

(−)-trans-3-*Bromo*-4-*hydroxy*-1,2,3,4-*tetrahydrophenanthrene* (6).—Bromohydrin (−)-(6) was prepared in 98% yield from (−)-(7a), $[\alpha]_D$ −174°, by the diborane method; [10-12] m.p. 151—152 °C (lit.,[2] racemic, m.p. 157—158 °C), $[\alpha]_D$ −68°.

(+)-1,2,3,4-*Tetrahydrophenanthrene* 3,4-*Oxide* (8).—(−)-3-Bromo-4-hydroxy-1,2,3,4-tetrahydrophenanthrene (6) (0.38 g), $[\alpha]_D$ −68°, and Amberlite (IRA-400 C. P., Mallinckrodt) ion-exchange resin in hydroxide anion form (3.0 g, prepared by washing with 1M-NaOH solution, water, and dry tetrahydrofuran) were stirred together in dry tetrahydrofuran (50 ml) at room temperature under an atmosphere of argon for 18 h. The resin was filtered off and the filtrate yielded crystals on concentration. Recrystallisation from light petroleum (b.p. 40—60 °C) gave colourless prisms of (8) (0.25 g, 93%); m.p. 51 °C, $[\alpha]_D$ +156° (Found: C, 85.6; H, 6.1. $C_{14}H_{12}O$ requires C, 85.7; H, 6.1%).

(+)-trans-3,4-*Dihydroxy*-1,2,3,4-*tetrahydrophenanthrene* (11) *and* (−)-cis-3,4-*Dihydroxy*-1,2,3,4-*tetrahydrophenanthrene* (12).—(+)-1,2,3,4-Tetrahydrophenanthrene 3,4-oxide (8) (0.038 g, $[\alpha]_D$ +156°) was dissolved in a mixture of tetrahydrofuran (7 ml), water (200 ml), and $NaClO_4$ (9 g) at pH 3 and was allowed to stand at room temperature for 18 h under argon. The mixture was extracted with ethyl acetate (200 ml), washed with saturated NaCl solution, dried ($MgSO_4$), and concentrated to yield a crystalline product mixture which was separated by h.p.l.c. [Dupont Zorbax ODS 9.4 mm × 25 cm column, methanol : water (60 : 40)]. The (+)-*trans*-diol (11) was isolated (0.033 g, 80%, *k* = 1.25) as crystals, m.p. 175—176 °C, $[\alpha]_D$ +25° (dioxan) (Found: C, 78.5; H, 6.5. $C_{14}H_{14}O_2$ requires C, 78.5; H, 6.6%). The (−)-*cis*-diol (12) was found as the minor component (0.07 g, 17%, *k* 2.45), m.p. 168—169 °C (lit.,[2] m.p. 168—169 °C), $[\alpha]_D$ +22° (dioxan).

(−)-3-*Hydroxy*-1,2,3,4-*tetrahydrophenanthrene* (14).—$LiAlH_4$ reduction of (+)-(8) ($[\alpha]_D$ +156°) gave a 97% yield of (−)-(14); m.p. 78—79 °C, $[\alpha]_D$ −49° (Found: C, 84.65; H, 7.3. $C_{14}H_{14}O$ requires C, 84.8; H, 7.1%).

(−)-trans-4-*Acetoxy*-3-*bromo*-1,2,3,4-*tetrahydrophenanthrene* (9a) *and* (−)-trans-3-*Bromo*-4-*trifluoroacetoxy*-1,2,3,4-*tetrahydrophenanthrene* (9b).—The bromo-esters (−)-(9a) and (−)-(9b) were prepared from samples of (−)-(6) ($[\alpha]_D$ −48° and −68° respectively) according to the literature method.[2]

(−)-4-Acetoxy-3-bromo-1,2,3,4-tetrahydrophenanthrene (9a) was isolated in 71% yield; m.p. 126—127 °C (lit.,[2] racemic m.p. 127—128 °C), $[\alpha]_D$ −70°.

(−)-3-Bromo-4-trifluoroacetoxy-1,2,3,4-tetrahydrophenanthrene (9b) was obtained in 90% yield, m.p. 117—118 °C (lit.,[2] racemic m.p. 115 °C), $[\alpha]_D$ −156° ($CHCl_3$).

(−)-4-*Acetoxy*-1,2,3,4-*tetrahydrophenanthrene* (10).—(−)-4-Acetoxy-1,2,3,4-tetrahydrophenanthrene (10) was prepared from (−)-(9a) ($[\alpha]_D$ −70°) by $LiAlH_4$ reduction followed by reaction with acetyl chloride to give a total yield of 24%; m.p. 104—105° (Found: C, 80.0; H, 6.7. $C_{16}H_{16}O_2$ requires C, 80.0; H, 6.7%), $[\alpha]_D$ −106° ($CHCl_3$).

(−)-4-*Acetoxy*-1,3-*dibromo*-1,2,3,4-*tetrahydrophenanthrene* (13a).—(−)-4-Acetoxy-1,3-dibromo-1,2,3,4-tetrahydrophenanthrene (13a) was prepared in 45% yield from (−)-(9a) ($[\alpha]_D$ −80°) by the literature method; [2] m.p. 154—155 °C (lit.,[2] racemic m.p. 157—158 °C), $[\alpha]_D$ −30°.

Phenanthrene 3,4-*Oxide* (3).—Phenanthrene 3,4-oxide (3) was synthesised by the literature method from (13a) or (13b)[2] and was generally obtained in yields of 30—60%. Compound (3) was recrystallized from a cooled solution of ether–light petroleum; m.p. 30—55 °C (lit.,[8] indefinite m.p.). Using the method previously reported,[8] the arene oxide product (3) obtained from (13a) or (13b) after a reaction time of 20 h showed no optical rotation over the wavelength range 365—589 nm. However, optical activity in (3) was detected after a shorter reaction time (6 h). The results obtained using a range of samples of (9a) and (9b) of varying optical purity are summarized in Table 2. The immediate precursors of arene oxide (3), compounds (13a) and (13b), were less stable than (9a) or (9b) and thus in some cases were converted directly into (3) without purification or $[\alpha]_D$ determination.

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