Synthesis and Thermal Racemization of the 3,4-Oxide Metabolite of Benzo[*c*]phenanthrene

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Both the racemic form and the (−)-(3*R*,4*S*)-enantiomer of benzo[*c*]phenanthrene 3,4-oxide have been synthesized in 12 steps from naphthalene. The absolute stereochemistry of the arene oxide enantiomers and related chiral derivatives has been determined by n.m.r. methods. Spontaneous thermal racemization of (−)-benzo[*c*]phenanthrene 3,4-oxide occurred with a barrier to racemization ($\Delta G^{\neq}_{29\,°C}$ 24.6 kcal mol^{-1}) (1 kcal = 4.184 kJ) in accord with predictions based upon PMO calculations.

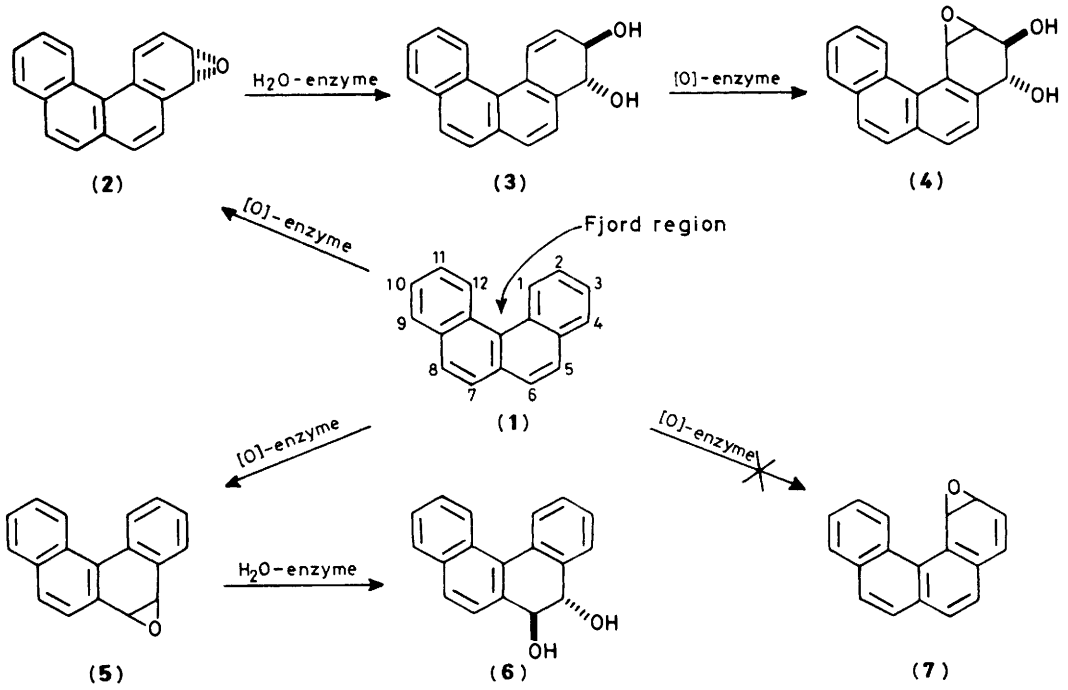
The polycyclic aromatic hydrocarbon (PAH) benzo[*c*]phenanthrene (**1**) is reported to be as prevalent in the environment as the intensively studied carcinogen benzo[*a*]pyrene.[1] Benzo[*c*]phenanthrene (**1**) differs however from benzo[*a*]pyrene by being a relatively weak carcinogen,[2] by having a fjord region between C-1 and C-12, and by being non-planar due to steric congestion about the fjord region.

The major metabolites of benzo[*c*]phenanthrene (**1**) obtained using rat liver microsomes, or a purified and reconstituted cytochrome P-450 system, are the K-region dihydrodiol (**6**) (77—89%), the 3,4-dihydrodiol (**3**) (6—17%), and small amounts of phenols (< 10%)[3] (Scheme 1). Based upon this metabolic profile, it is probable that the previously synthesized[4,5] K-region arene oxide (**5**) is the major initial metabolite. The arene oxide (**2**) has not previously been synthesized chemically but is clearly the metabolic precursor of the isolated *trans*-dihydrodiol (**3**).[3] To date the fjord region arene oxide, benzo[*c*]phenanthrene 1,2-oxide (**7**) does not appear to have been synthesized either chemically or enzymatically (based upon the virtual absence of the 1,2-dihydrodiol metabolite).[6,7]

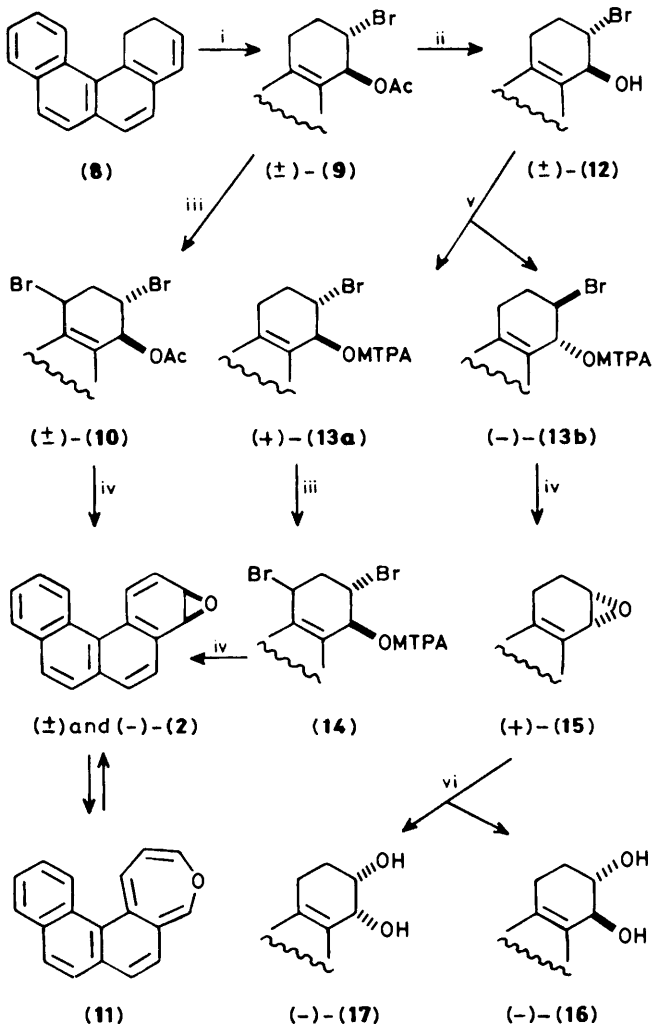
The results obtained from tumourogenicity[6,7] and mutagenicity[8] studies on the *trans*-3,4-dihydrodiol (**3**) and the 3,4-diol1,2-epoxides (**4**) suggest that (**3**) and (**4**) are proximate and ultimate carcinogens, respectively, produced during metabolism of benzo[*c*]phenanthrene (**1**). Predictions based upon the bay-region theory, suggest that arene oxide (**2**) [and thus the derived metabolites (**3**) and (**4**)] should be more carcinogenic than the isomeric K-region (**5**) or fjord region (**7**) arene oxides of benzo[*c*]phenanthrene (**1**).[9,10]

Previous studies, based upon PMO calculations,[11] led to the prediction that benzo[*c*]phenanthrene 3,4-oxide (3,4-epoxy-3,4-dihydrobenzo[*c*]phenanthrene) (**2**) enantiomers should racemize spontaneously *via* an oxepine valence tautomer (**11**) (Scheme 2). The barrier to racemization ($\Delta G^{\neq}_{t}$) was predicted to be of similar magnitude to that observed for chrysene 1,2-oxide ($\Delta G^{\neq}_{26\,°C}$, 23.1 kcal mol^{-1})[12] and chrysene 3,4-oxide ($\Delta G^{\neq}_{25\,°C}$, 24.4 kcal mol^{-1}) (1 kcal = 4.184 kJ).[13]

As part of a continuing study of the chemical and enzymatic synthesis, stereochemistry, and metabolism of arene oxides from these laboratories,[14] the synthesis of benzo[*c*]phenan-



Scheme 1.



Scheme 2. MTPA = $MeOC(CF_3)(Ph)CO$. i, *N*-Bromoacetamide–HOAc–LiOAc; ii, B_2H_6–THF; iii, *N*-bromosuccinimide; iv, NaOMe; v, MTPACl–pyridine; vi, dioxane–H_2O(pH 4.0)

threne 3,4-oxide (**2**) (both in racemic and optically active form) and thermal racemization studies are now reported.

1,2-Dihydrobenzo[*c*]phenanthrene (**8**) was obtained in nine steps from naphthalene (15% overall yield) using essentially the literature methods.[4,15] The bromoacetate (**9**) which was obtained in good yield (80%) from (**8**) by treatment with *N*-bromoacetamide in acetic acid, served as a stable precursor of arene oxide (**2**). Treatment of a racemic sample of (**9**) with *N*-bromosuccinimide resulted in benzylic bromination occurring in the fjord region to yield the dibromoacetate (**10**). Owing to instability, compound (**10**) was converted directly into benzo[*c*]phenanthrene 3,4-oxide (**2**) without purification. It is noteworthy that both the bromination [(**9**)→(**10**)] and dehydrobromination [(**10**)→(**2**)] steps occurring within the fjord region appeared to proceed under normal conditions despite the steric crowding effect. The racemic arene oxide (**2**) proved to be a remarkably stable oil under non-acidic conditions and was purified by preparative t.l.c. using triethylamine-washed silica gel. The arene oxide (**2**) showed the characteristic n.m.r. pattern of arene oxides in the PAH series, and upon treatment with benzoic acid was found to aromatize yielding a phenolic product

In order to obtain an optically active sample of the arene oxide (**2**), the diastereoisomeric 2-methoxy-2-phenyl-2-trifluoromethylacetate (MTPA) esters, (**13a**) and (**13b**), of the bromohydrin (**12**) were synthesized. The yield of the bromohydrin (**12**) obtained from 1,2-dihydrobenzo[*c*]phenanthrene (**8**) was found to be improved (to 56%) using the two step method, *i.e.* synthesis of the bromoacetate (**9**) and treatment with diborane. The bromo-MTPA esters, (**13a**) and (**13b**), were prepared in almost quantitative (96%) yield by the reaction of (**12**) with (−)-MTPA chloride in pyridine. The separation (>98%) of the bromo-MTPA diastereoisomers, (**13a**) and (**13b**), was achieved by preparative h.p.l.c. on a Zorbax Sil column [α 1.21, eluting with cyclohexane–diethyl ether (98:2)]. In contrast to the bromoacetate (**9**), the bromo-MTPA esters, (**13a**) and (**13b**), were found to be unstable on silica gel and some losses of material occurred during diastereoisomer separations using preparative h.p.l.c. The diastereoisomer (**13a**) ($[\alpha]_D$ +45.9°) which was eluted later from the h.p.l.c. separation (low R_f on t.l.c. analysis) was found to undergo normal benzylic bromination at C-1 despite the steric hindrance present in the fjord region. The dibromo-MTPA ester product (**14**), being again an unstable compound [*cf.* compound (**10**)], was directly treated with sodium methoxide to yield benzo[*c*]phenanthrene 3,4-oxide (**2**). After preparative t.l.c. purification, this liquid sample of the arene oxide (**2**) had an $[\alpha]_D$ value of −88.0°. Spontaneous thermal racemization was observed at ambient temperature (18 °C), but it proved to be more convenient to conduct the kinetic studies at a slightly higher temperature. The rate constants obtained at *ca.* 29 °C on three different samples of the arene oxide (**2**) were not totally reproducible and gave a narrow range of values (0.780—1.237 × 10^{-5} s^{-1}, $\Delta G^{\neq}$ 24.40—24.76 kcal mol^{-1}). Despite these minor variations, the observed spontaneous racemization of benzo[*c*]phenanthrene 3,4-oxide (**2**) and similarity in the magnitude of $\Delta G^{\neq}_t$ values to those earlier obtained for chrysene 1,2- and 3,4-oxides[12,13] provide further evidence that PMO predictions of configurational stability based upon the intermediacy of oxepines [e.g. (**11**)] during racemization[11] are valid. These observations also suggest that the degree of non-planarity associated with the benzo[*c*]phenanthrene ring system (due to steric hindrance within the fjord region) does not affect the PMO calculations (and conclusions drawn from them) to a significant degree. Unfortunately it has not to date proved possible to determine the optical purity of the partially racemized samples of optically active benzo[*c*]phenanthrene 3,4-oxide (**2**), or chrysene 1,2-,[12] or 3,4-[13] oxide.

The determination of absolute configuration of (−)-benzo[*c*]phenanthrene 3,4-oxide (**2**) was based upon stereochemical correlation with the bromo-MTPA esters (**13a**) and (**13b**) and with the *trans*-tetrahydrodiol (**16**). The general n.m.r. trends used for assignment of absolute configuration to a range of bromo-MTPA esters[16] were found to be present in the analogous compounds (**13a**) and (**13b**).

The late eluting (low R_f) isomer (**13a**) ($[\alpha]_D$ +45.9°) having a larger δ_H value for 3-H (4.67) and a larger coupling constant ($J_{3,4}$ 4.6 Hz) is assumed to have a (3*S*,4*S*) configuration. Conversely, the early eluting (high R_f) isomer (**13b**) ($[\alpha]_D$ −68.8°) having a smaller δ_H value for 3-H (4.56) and a smaller coupling constant ($J_{3,4}$ 4.4 Hz) will have a (3*R*,4*R*) configuration.

Treatment of the early eluting bromo-MTPA ester (**13b**) ($[\alpha]_D$ −68.8°) with sodium methoxide yielded the tetrahydroepoxide (**15**) ($[\alpha]_D$ +162.9°) which upon acid catalysed (pH 4) hydrolysis yielded a mixture of the *trans*-(**16**) and *cis*-(**17**) tetrahydrodiols. The major *trans*-diol product (**16**) formed under these conditions resulted from exclusive attack at the benzylic position of the epoxide ring. The (3*R*,4*R*) absolute stereochemistry for (+)−(**16**) has recently[17] been assigned on the basis of (i) the n.m.r. spectra of the bis-menthyloxyacetate diastereoisomers of (+)- and (−)-(**16**) and (ii) the c.d. curves obtained from the bis-*p*-*N*,*N*-dimethylaminobenzoate ester of (+)-(**16**). The latter[17] configurational assignment can now be

Table 1.

Compound	$[\alpha]_D$ (solvent)	Absolute stereochemistry
(**13a**)	+45.9° ($CHCl_3$)	3*S*,4*S*
(**13b**)	−68.8° ($CHCl_3$)	3*R*,4*R*
(**2**)	−88.0° ⟶ 0° ($CDCl_3$)[a]	3*R*,4*S*
(**15**)	+162.9° ($CHCl_3$)	3*S*,4*R*
(**16**)	−27.5° (THF)	3*S*,4*S*
(**17**)	−47.4° (THF)	3*S*,4*R*

[a] Spontaneous racemization.

used to confirm that the early eluting isomer (**13b**) ($[\alpha]_D$ −68.8°) has the (3*R*,4*R*) configuration. The *cis*-tetrahydrodiol (**17**) was formed as a minor component from the acid-catalysed hydrolysis of the tetrahydroepoxide (**15**). The absolute configuration of all chiral derivatives synthesized in the present study are given in Table 1.

On the assumption that the later diastereoisomer (**13b**) ($[\alpha]_D$ +45.9°) has a (3*S*,4*S*) configuration, then the predominant enantiomer present in the optically active sample of (**2**) ($[\alpha]_D$ −88.0°) must have a (3*R*,4*S*) configuration by stereochemical correlation. Again, based on the assumption that (as in all other reported examples) the arene oxide metabolite (**2**) undergoes epoxide hydrolase-catalysed hydration by exclusive attack at the non-benzylic position, then the (+)-(3*S*,4*R*) enantiomer of (**2**) appears to be the preferred enantiomer when formed enzymatically from benzo[*c*]phenanthrene by the cytochromes P-450 in mammalian liver.[6,7] In view of the rather long half-life ($t_{\frac{1}{2}}$ *ca.* 17 h) of the arene oxide in chloroform at 30 °C, it is presumed that the optically active arene oxide (**2**) formed in aqueous buffer at 37 °C would not suffer extensive racemization during the course of the short incubations (10 min).

Experimental

^{1}H N.m.r. spectra were recorded in a Bruker WH250 MHz instrument using $CDCl_3$ as solvent unless stated otherwise. Optical rotation measurements were determined using $CDCl_3$ or alternative solvents as specified in association with a Perkin-Elmer Model 241 automatic polarimeter. Kinetic studies of the racemization of benzo[*c*]phenanthrene 3,4-oxide (**2**) were carried out using the equipment and methods previously reported.[12,13] Light petroleum refers to the fraction b.p. 40—60 °C and ether refers to diethyl ether.

(±)-trans-4-*Acetoxy*-3-*bromo*-1,2,3,4-*tetrahydrobenzo*[c]-*phenanthrene* (**9**)—1,2-Dihydrobenzo[*c*]phenanthrene (**8**) (0.46 g, 2 mmol) was stirred with *N*-bromoacetamide (0.28 g, 2 mmol) and lithium acetate (0.46 g, 4.5 mmol) in acetic acid (20 ml) at room temperature for 1.5 h. The mixture was diluted with cold water and extracted with ether; concentration of the extract gave a crude product which was purified by chromatography on silica gel [eluted with benzene–light petroleum (70:30)]. The yield of *bromoacetate* (**9**) was 0.6 g (80%), m.p. 132 °C (from ether–light petroleum) (Found: C, 64.9; H, 4.7. $C_{20}H_{17}BrO_2$ requires C, 65.0; H, 4.6%); δ (250 MHz; $CDCl_3$) 2.16 (3 H, s, COMe), 2.22—2.49 (2 H, m, 2-H), 3.64—3.94 (2 H, m, 1-H), 4.57—4.63 (1 H, m, 3-H), 6.48 (1 H, d, *J* 4.7 Hz, 4-H), 7.36—7.95 (7 H, m, ArH), and 8.78—8.82 (1 H, m, ArH).

(±)-4-*Acetoxy*-1,3-*dibromo*-1,2,3,4-*tetrahydrobenzo*[c]-*phenanthrene* (**10**).—The bromoacetate (**9**) (0.2 g, 0.54 mmol) was refluxed (0.5 h) with *N*-bromosuccinimide (0.096 g, 0.6 mmol) in CCl_4 (20 ml). The product (**10**) obtained by filtration and concentration of the filtrate was a colourless solid (0.18 g, 74%) which decomposed during purification attempts, δ (90 MHz; $CDCl_3$) 2.36 (3 H, s, COMe), 2.67—3.30 (2 H, m, 2-H), 5.16—5.45 (1 H, m, 3-H), 6.44 (1 H, t, *J* 3.2 Hz, 1-H), 6.76 (1 H, d, *J* 8.1 Hz, 4-H), 7.39—8.00 (7 H, m, ArH), and 8.90—9.40 (1 H, m, ArH).

(±)-3,4-*Epoxy*-3,4-*dihydrobenzo*[c]*phenanthrene* (**2**).—The crude dibromoacetate (**10**) (0.18 g, 0.4 mmol) and sodium methoxide (0.25 g, 4.6 mmol) were stirred at 0 °C in tetrahydrofuran (THF) for 18 h. Cold water (20 ml) was added to the mixture and the product, the arene oxide (**2**), was extracted with ether. The ether extract was washed with aqueous potassium hydroxide, dried over potassium carbonate, and concentrated to yield the arene oxide (**2**) (0.04 g, 40%). Purification was effected by preparative t.l.c. in triethylamine-washed silica gel using ether–light petroleum–triethylamine (15:80:5) as eluant. The arene oxide (**2**) (R_f 0.24) was obtained as a colourless gum (Found: M^+ 244.0887 5. $C_{18}H_{12}O$ requires 244.0888 1); δ (250 MHz; $CDCl_3$) 4.45—4.49 (1 H, m, 3-H), 4.81 (1 H, d, *J* 4 Hz, 4-H), 6.52 (1 H, dd, $J_{2,1}$ 9.8, $J_{2,3}$ 4 Hz, 2-H), 7.58—7.91 (8 H, m, 1-H and ArH), and 8.59—8.63 (1 H, m, ArH).

The arene oxide (**2**) appeared to be stable at ambient temperature but decomposed in the presence of benzoic acid to yield mainly 4-hydroxybenzo[*c*]phenanthrene.

(±)-trans-3-*Bromo*-4-*hydroxy*-1,2,3,4-*tetrahydrobenzo*[c]-*phenanthrene* (**12**).—To a solution of the bromoacetate (**9**) (0.4 g, 1.1 mmol) in dry THF under an atmosphere of nitrogen at 0 °C, was added borane–tetrahydrofuran complex (1M solution in THF; 1.2 ml). The reaction was stirred for 5.5 h and worked up by addition of water (20 ml) and extraction with chloroform to yield the bromohydrin (**12**) as a pale yellow solid (0.25 g, 70%) which was recrystallized from ether–pentane, m.p. 111—112 °C (Found: M^+ 326.0305 2. $C_{18}H_{15}OBr$ requires 326.0306 7); δ (90 MHz; $CDCl_3$), 2.12—2.56 (2 H, m, 2-H), 3.72 (2 H, m, 1-H), 4.41—4.69 (1 H, m, 3-H), 5.18 (1 H, d, *J* 7 Hz, 4-H), 7.40—8.00 (7 H, m, ArH), and 8.57 (1 H, m, ArH).

(−)-(3R,4R)-(**13b**) *and* (+)-(3S,4S)-(**13a**)-trans-3-*Bromo*-4-(2-*methoxy*-2-*phenyl*-2-*trifluoromethylacetoxy*)-1,2,3,4-*tetrahydrobenzo*[c]*phenanthrene*.—The bromohydrin (**12**) (0.15 g, 0.46 mmol) was dissolved in pyridine (0.4 ml) and stirred with (−)-MTPA chloride (0.20 g, 0.76 mmol) for 20 h at room temperature. Water was added and the mixture was extracted with ether. The product mixture [(**13a**)–(**13b**)] obtained after drying and concentrating the ether extract was a pale yellow oil (0.24 g, 96%) (Found: M^+ 542.0704 6. $C_{28}H_{22}BrF_3O_3$ requires 542.0704 8). The diastereoisomeric mixture [(**13a**)–(**13b**)] was separated (α 1.21) by preparative h.p.l.c. using cyclohexane–ether (98:2), a Dupont Zorbax Sil preparative column (20 × 250 mm), and a flow rate of 20 ml/min. The early isomer (**13b**) was isolated as a colourless oil (0.08 g, 32%); $[\alpha]_D$ −68.8° ($CHCl_3$); δ_H (90 MHz; $CDCl_3$), 2.23—2.30 (2 H, m, 2-H), 3.54 (3 H, m, OMe), 3.55—3.70 (2 H, m, 1-H), 4.54—4.60 (1 H, m, 3-H), 6.71 (1 H, d, *J* 4.4 Hz, 4-H), 7.28—8.00 (7 H, m, ArH), and 8.75—8.79 (1 H, m, ArH). The late isomer (**13a**) was also a colourless oil (0.07 g, 28%); $[\alpha]_D$ +45.9° ($CDCl_3$); δ_H (90 MHz; $CDCl_3$), 2.18—2.55 (2 H, m, 2-H), 3.64—3.68 (3 H, m, OMe), 3.69—3.89 (2 H, m, 1-H), 4.57—4.72 (1 H, m, 3-H), 6.68 (1 H, d, *J* 4.6 Hz, 4-H), 7.30—8.00 (7 H, m, ArH), and 8.75—8.79 (1 H, m, ArH).

(3S,4S)-1,3-*Dibromo*-4-(2-*methoxy*-2-*phenyl*-2-*trifluoro-methylacetoxy*)-1,2,3,4-*tetrahydrobenzo*[c]*phenanthrene* (**14**).—Benzylic bromination of the bromoester (**13a**) ($[\alpha]_D$ +45.9°; 0.21 g, 0.38 mmol) was carried out under similar conditions to those used for (**10**) to yield the unstable dibromoester (**14**) (0.2 g, 85%), δ (250 MHz; $CDCl_3$) 2.60—3.17 (2 H, m, 2-H), 3.86 (3 H, d, $J_{H,F}$ 1.4 Hz, OMe), 5.23—5.34 (1 H, m, 3-H), 6.32 (1 H, t, *J* 3.3 Hz,

1-H), 6.90 (1 H, d, *J* 8.2 Hz, 4-H), 7.20—7.97 (12 H, m, ArH), and 8.98—9.02 (1 H, m, ArH). This product was used directly in the synthesis of (−)-(**2**).

(−)-(3R,4S)-3,4-*Epoxy*-3,4-*dihydrobenzo*[c]*phenanthrene* (**2**).—The (3*S*,4*S*)-dibromo-MTPA ester (**14**) (0.18 g, 0.39 mmol) was treated with sodium methoxide and worked up in an manner identical with that used in the synthesis of (±)-(**2**). Preparative t.l.c. yielded (**2**) (0.019 g, 27%) as an oil; $[\alpha]_D$ −88.0° ($CHCl_3$). This optically active sample of (**2**) showed spectral characteristics identical with those of the racemic sample.

Spontaneous racemization of (−)-(**2**) occurred in solution at ambient temperature (18 °C) but kinetic studies were carried out using a $CDCl_3$ solution in a thermostatically controlled polarimeter cell operating at the slightly higher temperature of *ca.* 29 °C where racemization occurred at a more convenient rate. The samples appeared to be relatively pure by n.m.r. analysis both before and after racemization (*i.e.* no decomposition could be detected during racemization). In view of the problems of obtaining an ultra-pure sample of the liquid arene oxide (**2**), only a limited kinetic study was carried out which gave rate constants (k) and barriers to racemization ($\Delta G^{\neq}_{r}$) at *ca.* 29 °C for three samples of the optically active arene oxide (**2**) (Table 2). The rate constants and $\Delta G^{\neq}$ values showed a variation between samples which may be due to traces of impurities.

(+)-(3S,4R)-3,4-*Epoxy*-1,2,3,4-*tetrahydrobenzo*[c]*phenanthrene* (**15**).—The bromo-MTPA ester (**13b**) ($[\alpha]_D$ −68.8°; 0.19 g, 0.77 mmol) and sodium methoxide (0.2 g, 3.7 mmol) were stirred in THF (4 ml) at room temperature for 20 h. Addition of water (20 ml) and extraction with ether yielded the tetrahydroepoxide (**15**) as a colourless oil (0.083 g, 96%), $[\alpha]_D$ +162.9° ($CHCl_3$) (Found: M^+, 246.1045 8. $C_{18}H_{14}O$ requires M, 246.1044 6); δ (250 MHz; $CDCl_3$) 1.82—1.97 (1 H, m, 2-H), 2.50—2.60 (1 H, m, 2-H), 3.42—3.65 (2 H, m, 1-H), 3.81 (1 H, s, 3-H), 4.08 (1 H, d, *J* 4.4 Hz, 4-H), 7.51—7.91 (7 H, m, ArH), and 8.53—8.58 (1 H, m, ArH).

(−)-(3S,4S)-trans-3,4-*Dihydroxy*-1,2,3,4-*tetrahydrobenzo*[c]*phenanthrene* (**16**) *and* (−)-(3S,4R)-cis-3,4-*Dihydroxy*-1,2,3,4-*tetrahydrobenzo*[c]*phenanthrene* (**17**).—A solution of the (+)-tetrahydroepoxide (**15**) ($[\alpha]_D$ +162.9°, 0.08 g, 0.36 mmol) in dioxane (20 ml) was stirred at room temperature for 20 h with a buffer solution (15 ml, pH4) which was prepared by the addition of glacial acetic acid (2 drops) to a solution of sodium hydrogen phosphate (0.355 g, 2.5 mmol; in 100 ml water). The dioxane was removed under reduced pressure and the residue was extracted with warm $CHCl_3$. The dried and concentrated extract produced a mixture of the *trans*-(**16**) and *cis*-(**17**) tetrahydrodiols which were separated by preparative t.l.c. on silica gel using chloroform–methanol (96:4) as eluant and a multi-elution (× 3) procedure.

The low R_F (0.06) isomer was a crystalline solid (0.036 g, 42%) which was identified as (−)-(3*S*,4*S*)-*trans*-3,4-dihydroxy-1,2,3,4-tetrahydrobenzo[*c*]phenanthrene (**16**), m.p. 160—162 °C (from THF–pentane) (Found: M^+ 264.1151 3. Calc. for $C_{18}H_{16}O_2$ 264.1150 2); $[\alpha]_D$ −27.5° (THF) {lit.,[17] $[\alpha]_D$ 29.1° (THF)}; δ (250 MHz; [$^2H_8$]THF—D_2O) 1.66—1.79 (1 H, m, 2-H), 2.07—2.18 (1 H, m, 2-H), 3.55—3.66 (2 H, m, 1 H), 3.95—4.02 (1 H, m, 3-H), 4.65 (1 H, d, *J* 6.7 Hz, 4-H), 7.49—7.89 (7 H, m, ArH), and 8.76—8.80 (1 H, m, ArH).

(−)-(3*S*,4*R*)-*cis*-3,4-Dihydroxy-1,2,3,4-tetrahydrobenzo[*c*]-phenanthrene (**17**) was found to have a higher R_f value (0.13) by t.l.c. analysis on silica gel and was isolated by this method as a crystalline solid (0.01 g, 12%), m.p. 184—187 °C (from THF–pentane) (Found: M^+ 264.1153 9. $C_{18}H_{16}O_2$ requires 264.1150 2); $[\alpha]_D$ −47.4° (THF); δ (250 MHz; [$^2H_8$]THF—D_2O) 1.70—2.06 (2 H, m, 2-H), 3.45—3.85 (2 H, m, 1-H), 4.10—4.17 (1 H, m, 3-H), 4.82 (1 H, d, *J* 3.8 Hz, 4-H), 7.53—7.90 (7 H, m, ArH), and 8.82—8.85 (1 H, m, ArH).

Table 2.

Temperature (°C)	Rate constant k ($\times 10^{-5}$ s^{-1})	$\Delta G^{\neq}$ (kcal mol^{-1})
28.5	1.237	24.40
29.5	0.780	24.76
30.0	1.066	24.61

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