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Absolute Stereochemistry of *cis*-1,2-, *trans*-1,2-, and *cis*-3,4-Dihydrodiol Metabolites of Phenanthrene

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An unequivocal assignment of the absolute stereochemistry of *cis*-1,2- (**5a**) and *cis*-3,4- (**9a**) (bacteria) and *trans*-1,2- (**7a**) (rat) dihydrodiol metabolites of phenanthrene is described. The diacetates of these dihydrodiols are levorotatory. *cis*-1,2-Dihydroxy-1,2-dihydrophenanthrene (**5a**) was converted into (−)-2-acetoxy-1,2,3,4-tetrahydrophenanthrene (**3b**) by catalytic hydrogenation of the double bond and hydrogenolysis of the 1-acetoxyl group. The *S* configuration of C-2 in **3b** was assigned by application of the exciton chirality circular dichroism method to its corresponding benzoate **3c** and by chemical degradation of the methyl ether **3d** to (−)-dimethyl β-methoxyadipate (**4**) of known absolute configuration. The negative sign associated with the longest wavelength Cotton effect for the benzoate **3c** is consistent with the (1*R*,2*S*) configuration for the *cis*-dihydrodiol **5a.** The (1*R*,2*R*) and (3*S*,4*R*) configurations assigned to *trans*-1,2-dihydroxy-1,2-dihydro- (**7a**) and *cis*-3,4-dihydroxy-3,4-diydrophenanthrenes (**9a**), respectively, were obtained by use of the exciton chirality method on the monobenzoate derivatives of the corresponding tetrahydrodiols (**8b** and **8c** from **7a** and **10d** from **9a**). This is the first determination of the absolute stereochemistry of a bay region dihydrodiol.

Certain non-K region *trans*-dihydrodiol metabolites of carcinogenic polycyclic aromatic hydrocarbons (PAH's) such as benzo[*a*]pyrene[2] and benz[*a*]anthracene[3] have recently been shown to be highly carcinogenic and mutagenic on metabolic activation. These results have led to the formulation of the "bay region" theory (cf. **1**) which predicts carcinogenicity for specific PAH metabolites.[4] In this context optically active benzo[*a*]pyrene *trans*-7,8-dihydrodiols and the corresponding 7,8-diol 9,10-epoxides have been prepared and their absolute stereochemistry assigned.[5-7] Interestingly, all three of the metabolically formed *trans*-dihydrodiols of benzo[*a*]-pyrene, at the 4,5, 7,8, and 9,10 positions, are of high optical purity when formed from benzo[*a*]pyrene by rat liver microsomes.[8]

Metabolism of phenanthrene (**1**) is of considerable interest since it is the simplest hydrocarbon that has a "bay region". In addition, phenanthrene is known to be weakly carcinogenic on mouse skin.[9] Previous studies on the metabolism of phenanthrene have shown that it is converted in mammals to *trans*-1,2- (minor), 3,4- (trace), and 9,10- (major) dihydrodiols and in bacteria to *cis*-1,2- (minor) and 3,4- (major) dihydrodiols.[10] Among these metabolites, only the absolute stereochemistry of the (−)-(9*S*,10*S*)-*trans*-9,10-dihydrodiol **2** has been determined.[11] The present study unequivocally assigns absolute stereochemistry of the *cis*-1,2-, *cis*-3,4- and *trans*-1,2-dihydrodiols of phenanthrene by employing both the exciton chirality circular dichroism (CD) method and chemical degradation.

A particularly attractive compound for determining the absolute configurations of both *cis*- and *trans*-1,2-dihydroxy-1,2-dihdyrophenanthrenes would be 2-acetoxy-1,2,3,4-tetrahydrophenanthrene, since it could be readily obtained by catalytic hydrogenolysis of the diacetates of both 1,2-dihydrodiols. An optically active sample of authentic 2-hydroxy-1,2,3,4-tetrahydrophenanthrene was prepared as follows: diastereomeric *l*-menthyloxyacetates of *trans*-1-bromo-2-hydroxy-1,2,3,4-tetrahydrophenanthrene, obtained from 3,4-dihydrophenanthrene, were partially resolved by short-column chromatography.[12] Base treatment ($NaOCH_3$) of a fraction highly enriched in one of the less polar diastereomer ($[\alpha]_D$ −150° ($CHCl_3$)) gave (+)-1,2-epoxy-1,2,3,4-tetrahydrophenanthrene ($[\alpha]_D$ +82° ($CHCl_3$)), which was subsequently reduced by $LiAlH_4$ to (−)-2-hydroxy-1,2,3,4-tetrahydrophenanthrene (**3a,** $[\alpha]_D$ −71° ($CHCl_3$)). The acetate **3b** ($[\alpha]_D$ −50° ($CHCl_3$)) showed positive Cotton effects in its CD spectrum in the ca. 215–245-nm region with $\Delta\epsilon$ +8.5

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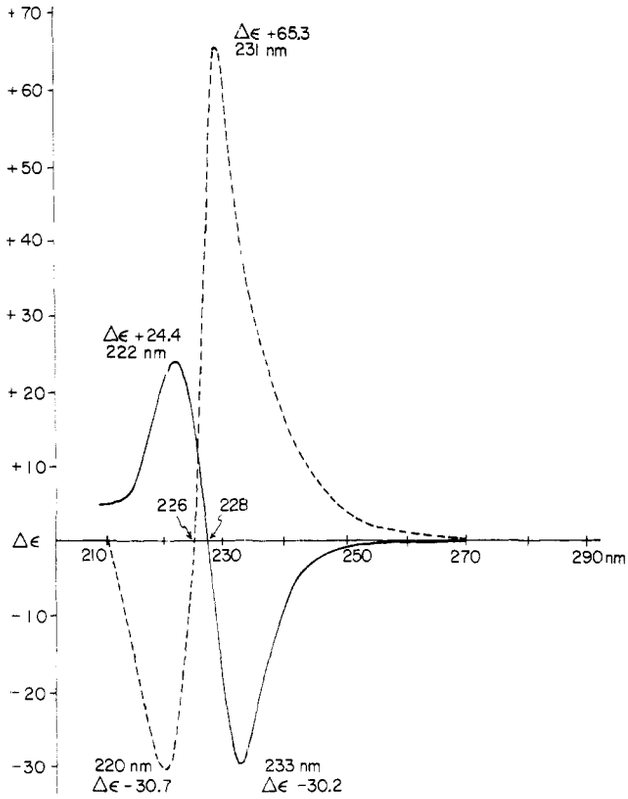


Figure 1. CD spectra of (*S*)-2-benzoyloxy-1,2,3,4-tetrahydrophenanthrene (**3c**) (-) and (3*S*,4*R*)-*cis*-3-hydroxy-4-benzoyloxy-1,2,3,4-tetrahydrophenanthrene (**10d**) (---) in MeOH/dioxane (9:1).

at 242 nm. The absolute configuration of the alcohol **3a** at C-2 was determined as *S* by applying the exciton chirality CD method[13-16] to its benzoyl derivative **3c**; $\Delta\epsilon_{233}$ −30 and $\Delta\epsilon_{222}$ +24, Figure 1. The strong $\pi \rightarrow \pi^*$ chromophores ascribable to the benzoyloxy group at 228 nm ($\epsilon \sim 12\,000$; intramolecular charge-transfer band[18]) and to the 1,2,3,4-tetrahydrophenanthrene moiety at 239 nm ($\epsilon \sim 100\,000$; $^1A \rightarrow {}^1B_b$ band[16]) are shown in Figure 2. The CD spectrum of **3c** shows a symmetric pair of Cotton effects centered at 228 nm (Figure 1) due to exciton splitting. Since the longest wavelength (first) Cotton effect at 233 nm is negative, the 2*S* absolute configuration is required. The cyclohexene ring conformation as well as the quasi-equatorial orientation of the benzoyloxyl group in **3c** were indicated from the NMR spectrum of **3c** (see Experimental Section).

Further evidence for the 2*S* configuration in alcohol **3a** ($[\alpha]_D$ −28° ($CHCl_3$)) was obtained by chemical degradation to (−)-dimethyl β-methoxyadipate (**4**) which is known to have the *S* configuration.[19] Thus, the methyl ether **3d** ($[\alpha]_D$ −37° ($CHCl_3$)) prepared from the alcohol **3a** with CH_3I/NaH was subjected to mild ozonolysis in $CHCl_3$ at −50 °C. Oxidative workup of the resulting ozonide with H_2O_2/HCOOH followed by treatment with diazomethane yielded *S*-(−)-dimethyl β-methoxyadipate (**4**, $[\alpha]_D$ −2.2° ($CHCl_3$)).

The structure of the microbial metabolite *cis*-1,2-dihydroxy-1,2-dihydrophenanthrene (**5a**) isolated as its acetate **5b** ($[\alpha]_D$ −1° ($CHCl_3$)) was determined by conversion into 2-acetoxy-1,2,3,4-tetrahydrophenanthrene. The diacetate **5b** was catalytically reduced (10% Pd-C) first to *cis*-1,2-diacetoxy-1,2,3,4-tetrahydrophenanthrene (**6**, $[\alpha]_D$ −193° (dioxane)) in ethyl acetate and then to 2-acetoxy-1,2,3,4-tetrahydrophenanthrene in acetic acid. This 2-acetoxy-1,2,3,4-tetrahydrophenanthrene showed positive CD peaks in the 215–245-nm region with $\Delta\epsilon_{240}$ +7.4 which allows assignment

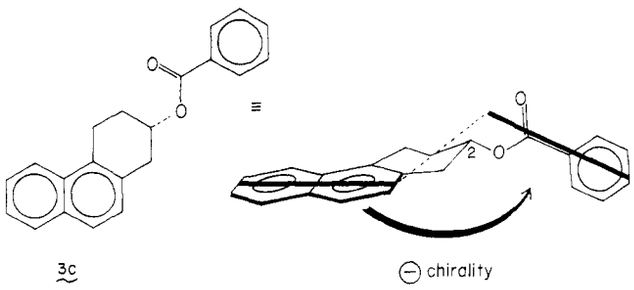
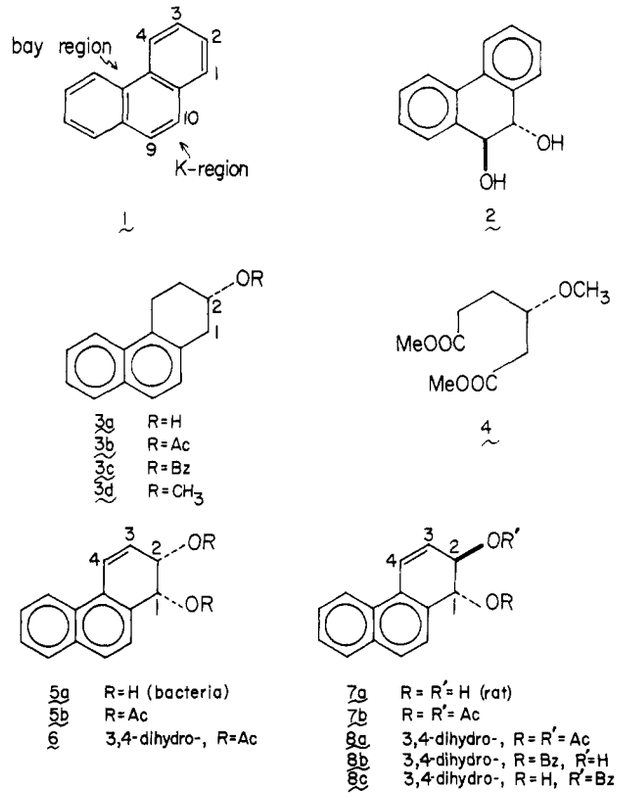


Figure 2. The stereostructure of (*S*)-2-benzoyloxy-1,2,3,4-tetrahydrophenanthrene (**3c**). Bold lines denote the electric transition dipole of the chromophore.

of 1*R*,2*S* stereochemistry to the *cis*-dihydrodiol **5a** and indicates that the bacterial dihydrodiol has reasonably high optical purity. Incubation of racemic phenanthrene 1,2-oxide with liver microsomes from phenobarbital-induced Sprague–Dawley rats (cf. ref 8) provided (−)-*trans*-1,2-dihydroxy-1,2-dihydrophenanthrene (**7a**) which was isolated as its diacetate **7b** ($[\alpha]_D$ −192° (dioxane)). Although reduction of **7b** smoothly produced (−)-*trans*-1,2-diacetoxy-1,2,3,4-tetrahydrophenanthrene (**8a**, $[\alpha]_D$ −39° (dioxane)), attempted hydrogenolysis of the 1-acetoxyl group under a variety of conditions did not cleanly remove the acetoxyl group without substantial reduction of the naphthalene system. Consequently the CD spectra of 1- and 2-monobenzoates (**8b** and **8c**, respectively) of the tetrahydrodiol derived from **8a** were examined. The negative and positive longest wavelength Cotton effects observed at 231 nm for **8b** and **8c**, respectively, require the 1*R*,2*R* configuration for the dihydrodiol **7a** based on the exciton chirality method.[11-14] Furthermore, the Δε values for these Cotton effects indicate that the *trans*-dihydrodiol metabolite **7a** has an ~30% optical purity.



The major bacterial metabolite of phenanthrene, the *cis*-3,4-dihydrodiol **9a** ($[\alpha]_D$ +58° (MeOH)), was isolated as its diacetate **9b** ($[\alpha]_D$ −204° (dioxane)). The above hydrogenation–hydrogenolysis sequence proved to be inadequate in that

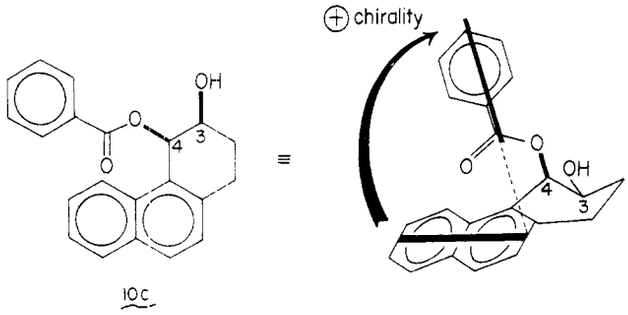
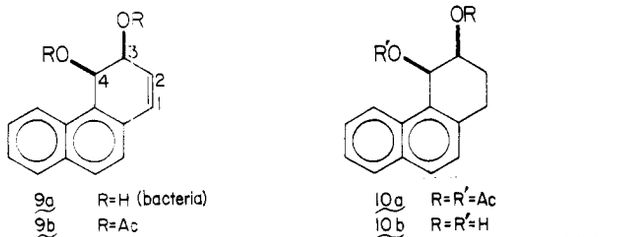
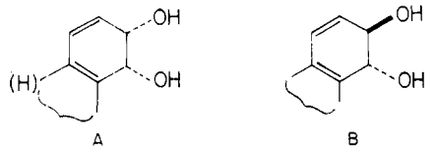


Figure 3. The stereostructure of (3*S*,4*R*)-*cis*-3-hydroxy-4-benzoyloxy-1,2,3,4-tetrahydrophenanthrene (**10d**). Bold lines denote the electric transition dipole of the chromophore. The alternative conformation which forms a *seven*-membered intramolecular hydrogen bond between the 3-OH and the carbonyl oxygen of the 4-benzoyloxy group would provide the same positive chirality.

the intermediate *cis*-3,4-diacetoxy-1,2,3,4-tetrahydrophenanthrene (**10a**) resisted several attempts to hydrogenolyze the acetoxyl group at C-4 under the conditions employed above. Although the exciton chirality CD spectrum of the 3,4-dibenzoate of **10b** should prove complex due to exciton interaction among the three chromophores, a monobenzoate derivative should show a CD spectrum which could be directly analyzed. Thus, treatment of the diol **10b** ($[\alpha]_D$ −21° (dioxane)) with trimethyl orthobenzoate in the presence of benzoic acid provided the benzyloxydioxolane **10c,** which was then hydrolyzed in AcOH/THF/H_2O at room temperature to *cis*-3-hydroxy-4-benzoyloxy-1,2,3,4-tetrahydrophenanthrene (**10d**). A related example of selective hydrolysis to the axial hydroxy ester of the *cis*-α-glycol has been reported.[20] Retention of the configuration at C-3 and C-4 in this conversion was validated by hydrolysis of the benzoate **10d** with mild base back to the original (−)-*cis*-3,4-diol **10b.** Typical exciton coupling was observed in the CD spectrum of the monobenzoate **10d,** $\Delta\epsilon_{231}$ +65.3 and $\Delta\epsilon_{220}$ −30.7 (Figure 1), indicative of the positive chirality between the naphthalene and 4-benzoyloxy chromophores (Figure 3). Therefore, the absolute configuration at C-4 in the benzoate **10d** is *R,ergo,* the 3*S*,4*R* stereochemistry in the orginal dihydrodiol **9a.** This is the first determination of the absolute stereochemistry of a bay-region dihydrodiol.



Notably, the absolute stereochemistry of the bacterial metabolites **5a** (1*R*,2*S*) and **9a** (3*S*,4*R*) from phenanthrene is common to the *cis*-dihydrodiols produced on bacterial metabolism of toluene,[21,22] naphthalene,[23] and anthracene.[24] All five *cis*-dihydrodiols share the common partial structure A, while the configuration in B (*R*,*R*) is the preferred enantiomer of the *trans*-1,2-dihydrodiols obtained on metabolism



of naphthalene in vivo in mammals or by the action of epoxide hydrase on naphthalene 1,2-oxide.[25] The enantiomeric preference for the urinary excretion of *trans*-1,2-dihydroxy-1,2-dihydroanthracene by mammals is species dependent (cf. ref 24). Microsomal epoxide hydrase from rabbit liver acts on racemic anthracene 1,2-oxide to produce a slight excess of the *R*,*R* enantiomer (as in B).[26] Administration of phenanthrene to rabbits leads to excretion of an excess of the (−)-*R*,*R* enantiomer of *trans*-1,2-dihydroxy-1,2-dihydrophenanthrene in the urine.[27] An excess of the same enantiomer was found when racemic phenanthrene 1,2-oxide was hydrated by rat liver microsomal epoxide hydrase in the present study. In vitro conversion of either benzo[*a*]pyrene or benzo[*a*]pyrene 7,8-oxide results in the formation of an excess of the (−)-(7*R*,8*R*)-dihydrodiol.[28] Thus all in vitro experiments which have examined the stereospecificity of epoxide hydrase on non-K-region arene oxides have found that an excess of the *R*,*R* enantiomer (B) is produced.

Experimental Section

Proton nuclear magnetic resonance spectra were measured in deuteriochloroform on Jeol MH-100 and Varian HA-100 instruments. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane as an internal standard with coupling constants (*J*) in hertz. Chemical ionization (NH_3 gas) and electron-impact mass spectra were run on a Finnigan Model 1015 gas chromatograph/mass spectrometer using the direct-inlet mode. Optical rotations were obtained at 23 °C using a Perkin-Elmer 141 automatic polarimeter, and circular dichroism spectra were recorded on a Cary 16 CD spectrometer. Analytical gas chromatography was carried out using a Pye-Unicam Model 104 instrument and a 2.5% silicon gum rubber column (2.5 m). Preparative GLC separations were carried out using identical column packing (6.3 m) and a modified Varian Autoprep (Model A-700).

Partial Resolution of (−)-2-Hydroxy-1,2,3,4-tetrahydrophenanthrene (3a). The optical resolution of 2-hydroxy-1,2,3,4-tetrahydrophenanthrene was carried out via the bromohydrin *l*-menthyloxyacetates.[10] *l*-Menthyloxyacetyl derivatives of *trans*-1-hydroxy-2-bromo-1,2,3,4-tetrahydrophenanthrene were partially resolved by short silica gel column chromatography and then converted via lithium aluminum hydride reduction of the corresponding epoxides (formed by base treatment of the partially separated diastereomers) to 2-hydroxy-1,2,3,4-tetrahydrophenanthrenes: mass spectrum (CI-NH_3) of (−)-enantiomer **3a** *m/e* 216 (M^+ + 18).

A summary of the optical rotations (all in $CHCl_3$) derived from two separate chromatography fractions is: *trans*-1-*l*-menthyloxyacetoxy-2-bromo-1,2,3,4-tetrahydrophenanthrene ($[\alpha]_D$ −150° or −60°) → 1,2-epoxy-1,2,3,4-tetrahydrophenanthrene ($[\alpha]_D$ +82° or +45°) → **3a** ($[\alpha]_D$ −71° or −28°).

(−)-2-Methoxy-1,2,3,4-tetrahydrophenanthrene (3d). To a stirred suspension of 1.20 g (25 mmol) of 50% sodium hydride (washed with hexane prior to use) in 50 mL of dry benzene at room temperature was added dropwise a solution of **3a** (1.13 g, 5.7 mmol, $[\alpha]_D$ −28° ($CHCl_3$)) in 50 mL of dry benzene under nitrogen. The reaction mixture was refluxed for 1 h and cooled prior to the slow addition with stirring of methyl iodide (20.0 g, 140 mmol). After refluxing for 21 h, the mixture was cooled to room temperature, poured into ice-cooled water, extracted with petroleum ether (bp range 40–60 °C), dried (Na_2CO_3), and concentrated to yield a red-brown oil, which was further purified by distillation to give 0.93 g of pale-yellow oil **3d:** bp 116–118 °C (0.22 mm), $[\alpha]_D$ −37° (*c* 1.80, $CHCl_3$).

Anal. Calcd for $C_{15}H_{16}O$: C, 84.87; H, 7.60. Found: C, 85.10; H, 7.70.

Ozonolysis of 3d. An ozone–oxygen mixture (BOC cryoproducts Mark II ozonizer) was passed for 3 h into a solution of 900 mg of **3d** in 50 mL of a chloroform/methanol mixture (1:1) maintained at a temperature of ca. −50 to −40 °C. Removal of the solvent in vacuo at room temperature produced a colorless oil which was then refluxed with 5 mL of 95% formic acid and 2.5 mL of 30% hydrogen peroxide for 8 h. Concentration of the reaction product under reduced pressure produced a viscous red oil which was dissolved in 20 mL of ethanol and treated with excess diazomethane (generated in situ from 5 g of Diazald and 0.8 g of KOH) in 40 mL of ether. The resultant crude product was analyzed by analytical GLC and was found to consist of three major components in the ratio of 2.9:1.1:1.0. Isolation of the second and third major peaks by preparative GLC and comparison

of these components with authentic samples[10] by GLC retention time, IR, MS, and NMR showed the second peak to be dimethyl β-methoxyadipate (**4**, 4.0 mg, $[\alpha]_D$ −2.2° (*c* 0.40, $CHCl_3$)) and the third peak to be dimethyl phthalate.

(−)-2-Acetoxy-1,2,3,4-tetrahydrophenanthrene (3b). The optically active alcohol **3a** ($[\alpha]_D$ −71° ($CHCl_3$), 5 mg) was dissolved in 0.30 mL of pyridine and treated with 0.15 mL of acetic anhydride. After 12 h at room temperature, the solvent was evaporated under reduced pressure. The semiliquid residue was purified by preparative TLC developed by CH_2Cl_2 to yield 6 mg of pure acetate **3b:** $[\alpha]_D$ −50° (*c* 0.262, $CHCl_3$); CD (MeOH) $\Delta\epsilon_{242}$ +8.5; mass spectrum (EI) *m/e* 240 (M^+).

2-Benzoyloxy-1,2,3,4-tetrahydrophenanthrene (3c). To a stirred solution of 9 mg of the alcohol **3a** in 0.3 mL of pyridine was added 0.15 mL of benzoyl chloride at 4 °C. The reaction mixture was kept at room temperature for 16 h, poured into ice-cooled water, and extracted twice with ethyl acetate. The combined organic layer was washed twice with aqueous $CuSO_4$ solution and once with water and dried, and the solvent was evaporated under reduced pressure. The residue thus obtained was purified by preparative silica gel TLC developed by 1% ethyl acetate in benzene to give 7 mg of the benzoate **3c:** mass spectrum (CI-NH_3) *m/e* 320 (M^+ + 18), 180 (M^+ − $C_6H_5CO_2H$); NMR δ 2.34 (m, 2 H, H-3), 3.32 (m, 4 H, H-1 and H-4), 5.58 (m, $\Delta W_{1/2}$ = 18 Hz), and 7.16–8.10 (11 H, aromatic protons).

(−)-*cis*-1,2-Diacetoxy-1,2,3,4-tetrahydrophenanthrene (6). (−)-*cis*-1,2-Diacetoxy-1,2-dihydrophenanthrene (**5b**, 4.1 mg) dissolved in 2 mL of dioxane was reduced catalytically in the presence of 10% Pd–C (10 mg) at room temperature for 40 min. The reaction mixture was diluted with 20 mL of ethyl acetate and the catalyst was removed by filtration. Evaporation of the solvent and purification by preparative TLC gave the tetrahydro derivative **6** (3.3 mg): $[\alpha]_D$ −193° (*c* 0.167, dioxane); mass spectrum (EI) *m/e* 298 (M^+), 238 (M^+ − AcOH), 196 (M^+ − AcOH − CH_2CO), 179, 178 (M^+ − 2 × AcOH), and 167; NMR δ 5.32 (d, t, H, H-2) and 6.31 (d, d, 1 H, H-1) with $^3J_{1eq,2ax}$ = 3.5 Hz, $J_{1eq,3eq}$ = 1.0 Hz, $^3J_{2ax,3eq}$ = 3.5 Hz, and $^3J_{2ax,3ax}$ = 10.5 Hz.

Hydrogenolysis of 6. Compound **6** (1.1 mg) was dissolved in 1.0 mL of acetic acid and treated with hydrogen at atmospheric pressure in the presence of 5 mg of 10% Pd–C. After 2 h another 5 mg of the catalyst was added to the reaction mixture. After 3 h at room temperature with stirring, the catalyst was removed by filtration and washed with 5 mL of ethyl acetate. The filtrate was diluted with water and extracted three times with ethyl acetate. The combined organic layer was washed twice with saturated aqueous $NaHCO_3$ and once with water and dried (Na_2SO_4), and the solvent was evaporated. Purification by preparative TLC gave pure **3b** (0.29 mg): CD (MeOH) $\Delta\epsilon_{240}$ +7.4.

(−)-*trans*-1,2-Diacetoxy-1,2,3,4-tetrahydrophenanthrene (8a). (−)-*trans*-1,2-Diacetoxy-1,2-dihydrophenanthrene (**7b**, $[\alpha]_D$ −192° (dioxane), 13 mg) dissolved in 6 mL of dioxane was reduced catalytically in the presence of 10% Pd–C (20 mg) at room temperature for 40 min. The reaction mixture was diluted with 40 mL of ethyl acetate and the catalyst was removed by filtration. Evaporation of the solvent and purification by preparative TLC gave the tetrahydro derivative **8a** (11 mg): mp 120–121 °C; $[\alpha]_D$ −39° (*c* 0.176, dioxane); mass spectrum (CI-NH_3) *m/e* 316 (M^+ + 18), 238 (M^+ − AcOH), 196 (M^+ − AcOH − CH_2CO); NMR δ 1.98 and 2.08 (both s, 3 H, OAc), 2.18 (m, 2 H, H-3), 3.16 (apparent t, 2 H, H-4), 5.27 (m, 1 H, H-2), 6.20 (d, 1 H, H-1), and 7.2–8.0 (6 H, aromatic protons) with $^3J_{1,2}$ = 6.0 Hz.

1-Benzoate (8b) and 2-Benzoate (8c) of (+)-*trans*-1,2-dihydroxy-1,2,3,4-tetrahydrophenanthrene. The diacetate **8a** (9 mg) was dissolved in 0.3 mL of tetrahydrofuran and diluted with 1 mL of methanol. The solution was treated with 0.3 mL of 1N aqueous sodium hydroxide in an ice bath and allowed to warm up to room temperature. After 2 h, the mixture was diluted with ~10 mL of water and extracted four times with 20-mL portions of ethyl acetate. The combined organic layer was washed with water, dried (Na_2SO_4), and evaporated under vacuum to dryness. The solid residue after recrystallization from ethyl acetate afforded pure (+)-*trans*-1,2-dihydroxy-1,2,3,4-tetrahydrophenanthrene (6.5 mg): mp 170–172 °C; $[\alpha]_D$ +10° (*c* 0.116, dioxane). This diol (5.5 mg) was dissolved in 0.1 mL of dry pyridine and diluted with 1 mL of dry methylene chloride. The solution was treated with 6.1 mg of benzoyl chloride (1.7 mol equiv) at 0 °C and allowed to warm up to room temperature. After 24 h, 20 μL of methanol was added and the solvent was evaporated to dryness under high vacuum. The oily residue was then purified by preparative TLC (developed with cyclohexane/ethyl acetate, 2:1) to yield 1-benzoate **8b** (2.0 mg) and 2-benzoate **8c** (2.2 mg), **8b**: mp 157–158 °C; NMR δ 4.22 (m, 1 H, H-2) and 6.18 (d, 1 H, H-1) with $^3J_{1ax,2ax}$ = 6.5 Hz; CD (MeOH/dioxane, 9:1) $\Delta\epsilon_{231}$ −14.2, $\Delta\epsilon_{226}$ 0, and $\Delta\epsilon_{222}$ +11.0. **8c**: mp 191–193 °C; NMR δ 4.92 (d, 1 H, H-1) and 5.32 (m, 1 H, H-2) with $^3J_{1ax,2ax}$ = 6.0 Hz; CD (MeOH/dioxane, 9:1) $\Delta\epsilon_{231}$ +12.5, $\Delta\epsilon_{227}$ 0, and $\Delta\epsilon_{222}$ −6.8.

(−)-*cis*-3,4-Diacetoxy-1,2,3,4-tetrahydrophenanthrene (10a). (−)-*cis*-3,4-Diacetoxy-3,4-dihydrophenanthrene (**9b**, $[\alpha]_D$ −204° (*c* 3.03, dioxane), 50 mg) dissolved in 10 mL of dioxane was reduced catalytically (30 mg of 10% Pd-C) at room temperature for 30 min. The mixture was diluted with 50 mL of ethyl acetate and the catalyst removed by filtration. Evaporation of the solvent and purification by preparative TLC gave the tetrahydro diacetate **10a** (40 mg): mp 123–124 °C; $[\alpha]_D$ −214° (*c* 3.14, dioxane); mass spectrum (CI-NH_3) *m/e* 316 (M^+ + 18); NMR δ 2.07 and 2.10 (both s, 3 H, OAc) 2.3 (m, 2 H, H-2), 3.1 (m, 2 H, H-1), 5.22 (d, t, 1 H, H-3), and 6.93 (d, 1 H, H-4) with $^3J_{2eq,3ax}$ = $^3J_{3ax,4eq}$ = 3.5 Hz and $^3J_{2ax,3ax}$ = 10.5 Hz.

(−)-cis-3,4-Dihydroxy-1,2,3,4-tetrahydrophenanthrene (10b). (−)-*cis*-3,4-Diacetate **10a** (25 mg) was dissolved in 0.5 mL of tetrahydrofuran and diluted with 1.5 mL of methanol. The solution was treated with 0.5 mL of 2 N aqueous sodium hydroxide in an ice bath and allowed to warm up to room temperature, and the mixture was kept at room temperature for 2 h. The reaction mixture was then diluted with ca. 20 mL of water and extracted four times with 40-mL portions of ethyl acetate. The combined organic layer was washed once with 50 mL of water, dried over Na_2SO_4, and evaporated under vacuum. The solid residue was recrystallized from ethyl acetate to yield pure **10b** (18 mg): mp 168–169 °C; mass spectrum (EI) *m/e* 214 (M^+); $[\alpha]_D$ −21° (*c* 0.578, dioxane); NMR δ 3.96 (m, $\Delta W_{1/2}$ = 22 Hz, 1 H, H-3) and 5.37 (t, 1 H, H-4) with $^3J_{ax,4eq}$ = $^4J_{2eq,4eq}$ = 3.6 Hz. Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.60; H, 6.87.

***cis*-3-Hydroxy-4-benzoyloxy-1,2,3,4-tetrahydrophenanthrene (10d).** A suspension of 12 mg of (−)-*cis*-3,4-diol **10b** and 5 mg of benzoic acid in 0.5 mL of trimethyl orthobenzoate was heated at 100 °C for 2 h. The course of reaction was followed by silica gel TLC (2% MeOH in CH_2Cl_2). Excess trimethyl orthobenzoate and methyl benzoate formed in the reaction were evaporated under vacuum. The orange-colored oily residue **10c** was then dissolved in 1 mL of tetrahydrofuran and 0.25 mL of water and treated with three drops of acetic acid and one drop of concentrated HCl. After 2 days, the reaction mixture was diluted with 10 mL of H_2O and extracted three times with 15-mL portions of ethyl acetate. The combined organic layer was washed with 40 mL of water, dried over K_2CO_3, and evaporated under vacuum to yield semisolid residue (13 mg). Purification by preparative TLC using 0.5% MeOH in $CHCl_3$ as a developing solvent provided 7 mg of pure **10d:** mass spectrum (CI-NH_3) *m/e* 336 (M^+ + 18), 300 (M^+ − H_2O), 196 (M^+ − C_6H_5COOH − H_2O); NMR δ 2.3 (m, 2 H, H-2), 3.18 (m, 2 H, H-1), 4.33 (d, t, 1 H, H-3), 7.09 (d, 1 H, H-4), and 7.3–8.1 (11 H, aromatic protons) with $^3J_{2eq,3ax}$ = 4.0 Hz, $^3J_{2ax,3ax}$ = 11.5 Hz, and $^3J_{3ax,4eq}$ = 4.0 Hz.

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Registry No.–3a, 64036-29-9; **3b,** 64036-30-2; **3c,** 64036-31-3; **3d,** 64036-32-4; **4,** 16859-76-0; **5a,** 64069-86-9; **5b,** 64069-87-0; **6,** 64069-88-1; **7a,** 64069-83-6; **7b,** 64069-84-7; **8a,** 64069-85-8; **8b,** 65484-16-4; **8c,** 65484-17-5; **9a,** 60966-01-0; **9b,** 60917-40-0; **10a,** 64069-89-2; **10b,** 64069-90-5; **10c,** 64036-26-6; **10d,** 64036-27-7; (+)-1,2-epoxy-1,2,3,4-tetrahydrophenanthrene, 64069-91-6; *trans*-1-*l*-menthyloxyacetoxy-2-bromo-1,2,3,4-tetrahydrophenanthrene isomer I, 64036-28-8; *trans*-1-*l*-menthyloxyacetoxy-2-bromo-1,2,3,4-tetrahychophenanthrene isomer II, 64069-92-7; methyl iodide, 74-88-41; benzoyl chloride, 98-88-41.

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Stereoselective Total Synthesis of Racemic Acorone

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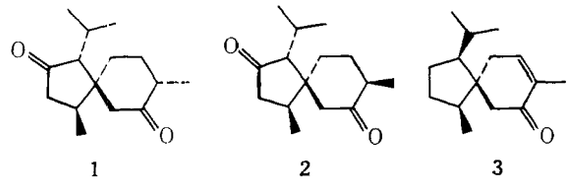
An efficient, stereoselective total synthesis of the acorane sesquiterpenes, (±)-acorone (1) and (±)-isoacorone (2), has been achieved. The synthetic approach, which utilizes a newly developed procedure for the spiroannulation of a cyclopentenone ring, commences with the alkylation of the pyrrolidine enamine (10) of 4-methyl-3-cyclohexene-1-carboxaldehyde with 3-iodo-2-chloropropene. Mercuric ion promoted hydrolysis of the vinyl halide 13 thus produced gave the γ-keto aldehyde 14, which underwent smooth, base-catalyzed cyclization to give the key intermediate, 8-methylspiro[4.5]deca-1,7-dien-3-one (15). Condensation of the enolate generated from compound 15 with acetaldehyde followed by the acid-catalyzed dehydration of the aldols gave a 47:53 mixture of (*E*)- and (*Z*)-1-ethylidene-8-methylspiro[4.5]deca-3,7-dien-2-one (17a and 17b, respectively). After the introduction of the two remaining methyl groups by a facile, one-pot procedure involving two successive treatments of 17a and 17b with lithium dimethylcuprate, followed by hydroboration and direct oxidation, a mixture consisting primarily of (±)-acorone (1) and (±)-isoacorone (2) was obtained. Separation of this mixture by preparative high-pressure liquid chromatography afforded the pure racemic natural products.

The greatest obstacle to the synthesis of the acorane sesquiterpenes such as acorone (1), isoacorone (2), and acorenone B (3) is the stereocontrolled construction of the spirocyclic carbon skeleton. A successful synthesis of these spiro sesquiterpenes depends critically, therefore, upon the generation of a quaternary carbon center which is suitably substituted for the direct annulation to a functionalized spiro[4.5]decane that may be subsequently elaborated to the target natural product. Although several syntheses of acorone (1) and isoacorone (2) have been reported,[1] the primary synthetic interest has been in acorenone B (3).[2] We now wish to report a highly stereoselective synthesis of racemic acorone and racemic isoacorone using a new approach for the spiroannulation of a cyclopentenone ring.[3]



1 2 3

As part of a general synthetic program, we have been interested in developing new synthetic methods for the construction of quaternary carbon atoms which bear dissimilarly functionalized alkyl appendages. We have recently discovered one particularly attractive procedure for the geminal alkylation at a carbonyl carbon atom that involves the direct conversion of ketones into the enamines of the homologous aldehydes.[4] These enamines are useful synthetic intermediates and may be employed without purification in subsequent reactions with electrophiles. For example, by the appropriate choice of electrophiles, this general synthetic procedure, which is depicted in eq 1, may be exploited for the preparation of α-allyldialkyl aldehydes,[4a] 4,4-disubstituted cyclohexenones,[4b] and 4,4-disubstituted cyclopentenones.[4c] When the starting ketone is cyclic, the latter two methods allow for the facile spiroannulation of cyclohexenones and cyclopentenones.

Our initial approach to the synthesis of acorone (1), shown in Scheme I, was based upon our new method for the spiroannulation of cyclopentenones and began with the ethylene glycol monoketal of cyclohexane-1,4-dione 4.[5] Thus, reaction

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