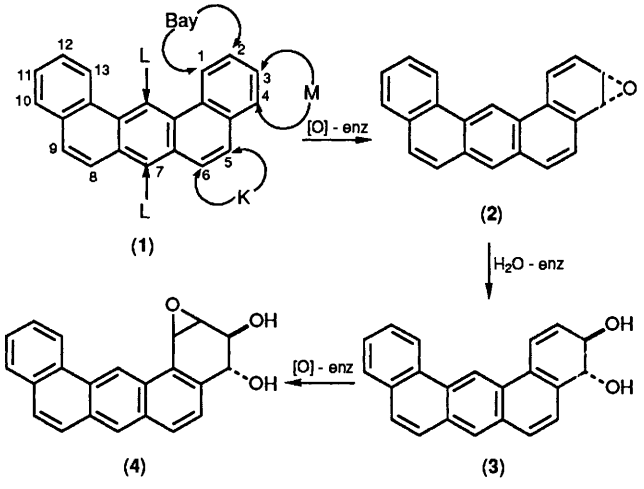
Synthesis of the Mammalian Metabolites of Dibenz[*a,j*]anthracene: Dibenz[*a,j*]anthracene 3,4-Oxide and (−)-(3*R*,4*R*)-*trans*-3,4-Dihydroxy-3,4-dihydrodibenz[*a,j*]anthracene

Derek R. Boyd* and Gerard A. O'Kane
Department of Chemistry, The Queen's University of Belfast, Belfast BT9 5AG

Dibenz[*a,j*]anthracene 3,4-oxide (**2**) and the isomeric oxepine (**19**) were synthesised simultaneously from a common dibromoester precursor (**9**). The oxepine isomer (**19**) was also formed by photoisomerisation of the arene oxide (**2**). Resolution and absolute configuration assignment of each enantiomer of *trans*-3-bromo-4-hydroxy-1,2,3,4-tetrahydrodibenz[*a,j*]anthracene (**10**) was achieved by chromatographic separation and recrystallisation of the MTPA diastereoisomers (**11a**/**11b**). The (+)-(3*S*,4*S*)bromo-MTPA ester (**11a**) was used in a seven-step synthesis of the chiral metabolite (−)-(3*R*,4*R*)-*trans*-3,4-dihydroxy-3,4-dihydrodibenz[*a,j*]anthracene (**3**). The (−)-(3*R*,4*R*)-bromo-MTPA ester diastereoisomer (**11b**) similarly served as a precursor of (3*S*,4*R*)-dibenz[*a,j*]anthracene 3,4-oxide (**2**) which spontaneously racemised *via* an unstable oxepine isomer (**18**).

Dibenz[*a,j*]anthracene (**1**) is a weakly carcinogenic symmetrical member of the polycyclic aromatic hydrocarbon (PAH) series[1] containing both bay-, K-, L-, and M-regions. It has been detected as a relatively minor component of coal fractions and may thus be liberated into the environment. Mono-oxygenase-catalysed epoxidation of dibenz[*a,j*]anthracene (**1**) in mammalian liver systems occurs at the M-region (3,4-bond) to yield the arene oxide (**2**) as a minor metabolite which is in turn enzymatically hydrated and epoxidized to yield the *trans*-diol (**3**) and 3,4-diol 1,2-epoxide (**4**)[2] respectively (Scheme 1). These 3,4-diol 1,2-epoxide metabolites (**4**) have recently been shown to form covalent adducts with DNA[2] and thus are considered to be the ultimate carcinogens of dibenz[*a,j*]anthracene in accordance with the bay-region theory of carcinogenesis.[3]



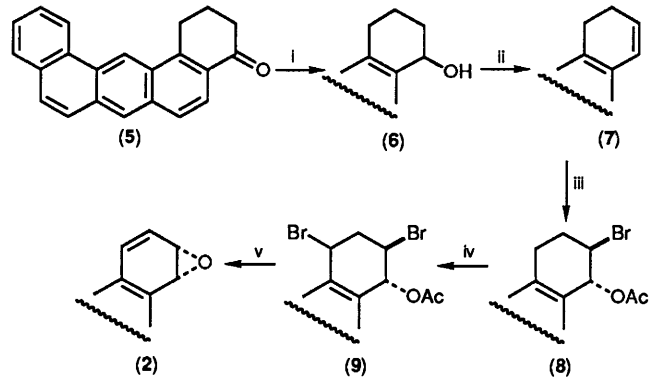
Scheme 1.

Prior to the preliminary communication of the synthesis of the arene oxide (**2**)[4] neither the latter compound nor the derived *trans*-dihydrodiol metabolite (**3**) had been chemically synthesised. In previous studies from these laboratories it had been predicted on the basis of simple PMO calculations that enantiomers of dibenz[*a,j*]anthracene 3,4-oxide (**2**) would spontaneously racemise.[5] It has also been observed previously that the absolute configurations of the arene oxide and *trans*-dihydro-diol metabolites of PAHs in mammalian liver systems (which mainly result from the combined action of cytochrome P-450c and epoxide hydrolase) have consistently had the (*R*)-configuration at the benzylic position, *i.e.* (*R,S*) and (*R,R*)-configurations, respectively, as shown in structures (A) and (B).[6]

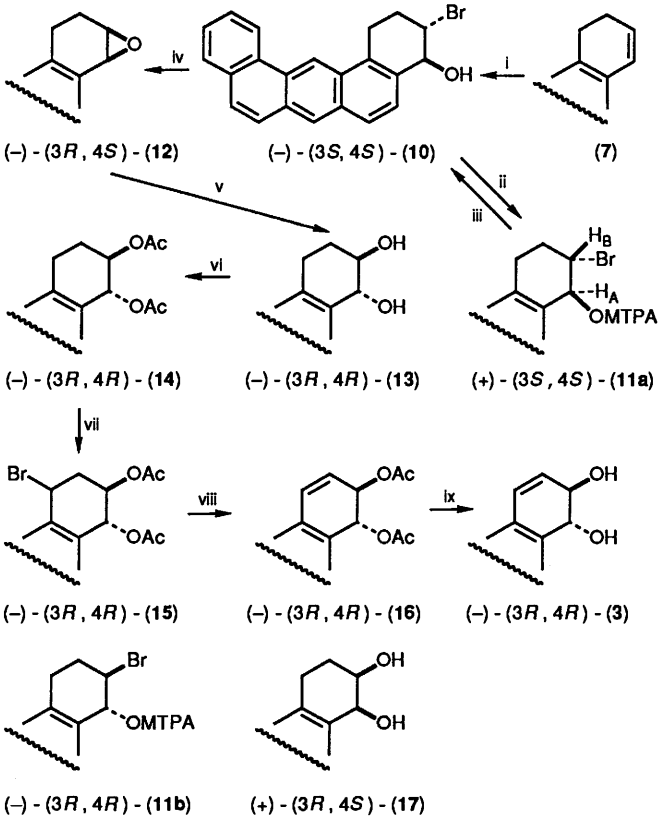
The present study was thus initiated in order (i) to synthesise (3*S*,4*R*)-benz[*a,j*]anthracene 3,4-oxide (**2**) and to check for spontaneous racemisation, (ii) to obtain evidence of the photoisomerisation of arene oxide (**2**) to a stable isomeric oxepine (**19**), and (iii) to synthesise the minor metabolite of dibenz[*a,j*]-anthracene (**1**), (−)-(3*R*,4*R*)-*trans*-3,4-dihydroxy-3,4-dihydrodibenz[*a,j*]anthracene (**3**), as an aid to assignment of metabolite structure and absolute configuration.

2,3-Dihydrodibenz[*a,j*]anthracene-4(1*H*)-one (**5**) was obtained in a multistep synthesis from 9,10-dihydrophenanthrene using essentially the literature route but with minor modifications.[7–10] The sequence of reactions from the ketone (**5**) to the arene oxide (**2**) (Scheme 2) is very similar to that used in the recent synthesis of benzo[*e*]pyrene 9,10-oxide[11] and involved (i) $NaBH_4$ reduction to yield the alcohol (**6**) (91%), (ii) acid-catalysed dehydration to yield the olefin (**7**) (71%), (iii) bromoacetate formation (**8**) (72%) using *N*-bromoacetamide (NBA) and LiOAc in tetrahydrofuran (THF)–AcOH solution, (iv) benzylic bromination using *N*-bromosuccinimide (NBS) to yield the dibromoacetate (**9**) (82%), and (v) cyclisation–dehydrobromination using NaOMe in THF to yield the racemic arene oxide (**2**) (84%) in associaton with the oxepine (**19**) (16%). The product mixture of arene oxide (**2**) and oxepine (**19**) was separated by preparative HPLC using diethyl ether–triethylamine–hexane (20:1:79) as eluant and each component was obtained as a pure crystalline compound with characteristic spectral features.[11]

Olefin (**7**) was also converted into the racemic bromohydrin



Scheme 2. *Reagents:* i, $NaBH_4$; ii, H^+; iii, NBA, LiOAc, AcOH; iv, NBS, CCl_4; v, NaOMe, THF.



Scheme 3. *Reagents:* i, NBA, THF; ii, (−)-MTPACl, pyridine; iii, Bu^i_2AlH; iv, OH^-; v, H^+, dioxane; vi, Ac_2O, pyridine; vii, NBS, CCl_4; viii, DBN; ix, NH_3 MeOH.

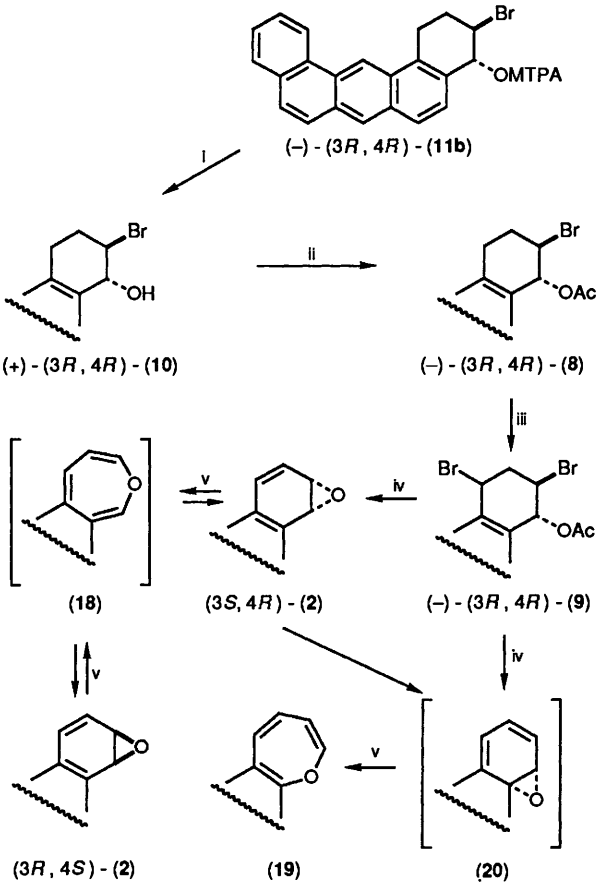
(**10**) in good yield (86%) by treatment with NBA in aqueous THF (Scheme 3). The bromohydrin enantiomers (**10**) were resolved by reaction with (−)-(*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropionyl (MTPA) chloride to yield the bromo-MTPA diastereoisomers (**11a**/**11b**). The latter diastereoisomeric mixture was separated by short column chromatography followed by fractional crystallization. The bromo-MTPA diastereoisomers (**11a**), $[\alpha]_D$ +68°, and (**11b**) $[\alpha]_D$ −99°, were shown to be pure by ^1H NMR spectral analysis, HPLC analysis, and by reduction using di-isobutylaluminium hydride (Dibal-H) to yield the bromohydrin enantiomers (**10**), $[\alpha]_D$ −94° and +94°, respectively.

The assignment of absolute configuration to the chiral bromo-MTPA derivatives (**11a**) and (**11b**) was made on the basis of the method previously used for other similar derivatives in the PAH series.[11,12] By analogy with the results obtained from over twenty similar resolved bromo-MTPA diastereoisomers (including nine whose absolute configurations have been unequivocally assigned by X-ray crystallography) a reliable chromatographic and NMR method has been found. Thus, using (−)-MTPA acid as resolving agent the bromo-MTPA diastereoisomer having a high R_f on silica gel TLC analysis, a shorter retention time on normal phase HPLC, a smaller positive δ_H value for the non-benzylic proton (H_B), and a smaller negative $\delta(^{19}F)$ value for the CF_3 group will have an (*R*,*R*)-configuration and *vice-versa* for the (*S*,*S*)-diastereoisomer. Using this method the bromo-MTPA ester (**11b**), $[\alpha]_D$ −99°, which showed a higher R_f value and a shorter HPLC retention time, had a smaller δ_H value for H_B (4.60δ), a smaller negative $\delta(^{19}F)$ value for CF_3 (−8.62 ppm), and a smaller coupling constant J_{AB} (3.7 Hz) was assigned to (3*R*,4*R*)-configuration. The lower R_f isomer (**11a**), $[\alpha]_D$ +68°, had spectral data [$\delta(H_B)$ 4.68, $\delta(CF_3)$ − 8.66 ppm, and J_{AB} 4.1 Hz] which were thus consistent with the (3*S*,4*S*)-configuration. The absolute configurations of the bromo-MTPA diastereoisomers (**11a**) and (**11b**) were thus stereochemically correlated with all other chiral compounds in Schemes 2 and 3 since the mechanisms of each interconversion is well established.

The (3*R*,4*R*)-bromo-MTPA diastereoisomer (**11b**), $[\alpha]_D$ −99°, was treated with Dibal-H in hexane to yield the (3*R*,4*R*)-enantiomer of the bromohydrin (**10**), $[\alpha]_D$ +94°, in 74% yield. Similar treatment of the (3*S*,4*S*)-diastereoisomer (**11a**), $[\alpha]_D$ +68° gave the (3*S*,4*S*)-enantiomer of the bromohydrin (**10**), $[\alpha]_D$ −94° (82%). The (+)-(3*R*,4*R*)-bromohydrin enantiomer (**10**) $[\alpha]_D$ +94°, was treated with acetic anhydride in pyridine to yield the (−)-(3*R*,4*R*)-bromoacetate (**8**), $[\alpha]_D$ −77°, in 70% yield. Using identical conditions to those outlined in Scheme 2 for the racemic form, the (−)-(3*R*,4*R*)-bromoacetate (**8**) ($[\alpha]_D$ −77°) was converted *via* the (−)-(3*R*,4*R*)-dibromoacetate (**9**), $[\alpha]_D$ −514°, into a mixture of the arene oxide (**2**) and oxepine (**19**) (65:35) in a total yield of 65%. The arene oxide (**2**) was found to be optically inactive ($[\alpha]_D$ 0°) (Scheme 4). This result is in accord with predictions[5] that the initially formed (3*S*,4*R*)-enantiomer of arene oxide (**2**) would spontaneously racemise *via* the unstable oxepine intermediate (**18**). A similar spontaneous racemisation had previously been predicted[5] and found[6] in the arene oxide derivatives of phenanthrene (1,2- and 3,4-), benz[*a*]anthracene (1,2- and 3,4-), chrysene (1,2- and 3,4-), benzo[*c*]phenanthrene (3,4-), triphenylene (1,2-), and benzo[*e*]pyrene (9, 10). In all cases it was assumed that the loss of resonance energy (ΔE_R) associated with the arene oxide ⇌ oxepine isomerisation, *e.g.* (**2**) ⇌ (**18**), was relatively low, *i.e.* ΔE_R < 15 kcal mol^{-1} (1 cal = 4.184 J). The PMO calculations[5] predicted that a value of ΔE_R = 7.9 kcal mol^{-1} would be expected for arene oxide (**2**).

While the unstable oxepine (**18**) considered to be responsible for spontaneous racemisation of the arene oxide enantiomers (**2**) was not detected, by contrast the relatively stable oxepine (**19**) could not be avoided as a product from the normal dibromoester route to the arene oxide (**2**). If formation of the isolable oxepine [*e.g.* (**19**)] is assumed to occur by electrocyclic rearrangement of the directly formed arene oxide intermediate (**20**), as suggested in earlier reports,[4,11] then a similar loss in resonance energy (ΔE_R) could be associated with the initial step in both racemisation [(**2**)→(**18**)→(**2**)] and oxepine formation [(**9**)→(**20**)→(**19**)].

An alternative explanation for the formation of the oxepine (**19**) is that an oxygen-walk process (sigmatropic rearrangement) of the arene oxide (**2**) to the unstable arene oxide (**20**) followed by electrocyclic rearrangement to the oxepine (**19**) has occurred. The loss of resonance energy associated with this oxygen-walk process [(**2**)→(**20**)] is again predicted to be similar to that associated with the isomerisation of the arene oxide (**2**) to the oxepine (**18**) (ΔE_R 7.9 kcal mol^{-1}). The observation that a pure



Scheme 4. *Reagents:* i, Bu^i_2AlH; ii, Ac_2O, pyridine; iii, NBS, CCl_4; iv, NaOMe, THF; v, heat.

sample of arene oxide (**2**) could be separated from the product mixture of (**2**) and the oxepine (**19**), and was found to exist in the arene oxide form only in $CDCl_3$ (in an NMR tube from which room light was excluded) for an extended period prior to aromatisation, appears to exclude a rapid spontaneous isomerisation process. Attempts to monitor the formation of arene oxide (**2**) when the dibromoacetate (**9**) was treated with $NaOCD_3$ in [$^2H_8$] THF solvent (NMR tube maintained at 0 °C, in the dark) by sequential ^1H NMR analysis showed a significant proportion of the oxepine (**19**) (12%) associated with arene oxide (**2**) (84%) and isomeric phenol(s) (4%) at the earliest stage of detection. The relative proportion of arene oxide (**2**) fell (to 19%) over a 2 day period as the proportions of the oxepine (**19**) (to 54%) and phenol(s) (to 27%) increased. After 3 days only the oxepine (**19**) and phenol(s) could be detected. The final analysis of the product mixture after 28 days showed only phenol(s). This experiment shows that the oxepine (**19**) was present at all stages of the reaction, that the arene oxide (**2**) decomposes more rapidly than the oxepine (**19**), and that both the arene oxide (**2**) and the oxepine (**19**) are unstable even under non-acidic conditions.

While no clear evidence for the thermal isomerisation of the arene oxide (**2**) to the oxepine (**19**) could be obtained, the photochemical rearrangement was found to occur very readily. Thus, a mixture of the arene oxide (**2**) (65%) and the oxepine (**19**) (35%) in a Pyrex NMR tube containing $CDCl_3$, when irradiated with UV light (> 300 nm) for 0.5 h, showed that all the original arene oxide (**2**) had rearranged to the oxepine (**18**) (67%) by a photochemical oxygen-walk process or had isomerized to phenol(s) (33%), by comparison with a reference compound (pentamethylbenzene). Since light was excluded during the original synthesis of the arene oxide (**2**) and the oxepine (**19**) from dibromo ester (**9**), it is unlikely that the oxepine product (**19**) was obtained by a photochemical oxygen-walk process.

The association of arene oxides [e.g. (**2**)] with the corresponding oxepines [*e.g.* (**19**)] during synthesis has now been found in the benz[*a*]anthracene,[4] benzo[*e*]pyrene,[4,11] triphenylene,[4] dibenz[*a,j*]anthracene,[4] dibenz[*a,h*]anthracene[4] and dibenz[*a,c*]anthracene[13] series (a total of seven examples) and is now a well established trend in arene oxides having a low ΔE_R value. To date no evidence of these stable oxepine isomers as metabolites of PAHs has been found.

A synthetic route to the expected major enantiomer of the *trans*-dihydrodiol metabolite of dibenz[*a,j*]anthracene (**3**) is outlined in Scheme 3. The synthetic pathway is very similar to that previously used with resolved bromohydrin enantiomers in the PAH series.[14,15]

The (3*S*,4*S*)-enantiomer of the bromohydrin (**10**), $[\alpha]_D$ −94°, was converted to the (3*R*,4*S*)-tetrahydroepoxide (**12**), $[\alpha]_D$ −88°, in 96% yield using a basic form of Amberlite IRA-900 resin. Acid-catalysed hydration of the epoxide (**12**), $[\alpha]_D$ −88°, in aqueous dioxane (pH 2.5) gave a mixture of the (3*R*,4*R*)-*trans*-tetrahydro-diol (**13**), $[\alpha]_D$ −31°, and the (3*R*,4*S*)-*cis*-tetrahydro-diol (**17**), $[\alpha]_D$ +173°, in a ratio of 3:1 and in a total isolated yield of 52% after PLC purification. The assignment of the (3*R*,4*R*)-absolute configuration of the *trans*-tetrahydro-diol (**13**) is based upon the well precedented assumption that ring opening will occur by nucleophilic attack and inversion of configuration at the benzylic oxirane ring position. Acetylation of the (3*R*.4*R*)-*trans*-tetrahydro-diol (**13**), $[\alpha]_D$ −31°, using acetic anhydride in pyridine, gave the (3*R*,4*R*)-*trans*-tetrahydro-diacetate (**14**), $[\alpha]_D$ −146° (62% yield). A mixture of two bromodiacetate isomers (**15**), $[\alpha]_D$ −343°, was produced in 85% yield by benzylic bromination occurring both *cis* and *trans* to each acetate group. This mixture was not separated owing to instability of the bromodiacetates (**15**) but was converted directly into the (3*R*,4*R*)-*trans*-dihydro-diacetate (**16**), $[\alpha]_D$ −165° (28% yield), using 1,5-diazabicyclo[4.3.0]non-5-ene (DBN). Treatment of the (3*R*,4*R*)-*trans*-dihydro-diacetate (**16**), $[\alpha]_D$ −165°, with ammonia in MeOH–THF gave the (3*R*,4*R*)-*trans*-dihydro-diol (**3**), $[\alpha]_D$ −194° (58% yield). Based upon previous liver microsomal metabolism results,[6] an excess of the (−)-(3*R*,4*R*) enantiomer of dihydro-diol should be expected for this minor metabolite.

Experimental

9,10-Dihydrophenanthrene used in the synthesis of the ketone (**5**) was obtained from the Aldrich Chemical Co. The procedure used was similar to that in the literature involving nine synthetic steps.[7–10] A modified Reformatsky reaction on 9,10-dihydrobenz[*a*]anthracen-11(10*H*)-one using methyl-4-bromocrotonate and amalgamated zinc gave a hydroxy ester intermediate in 83% yield. Dehydration of the latter compound yielded four isomeric diene esters which were converted to a common acid, 4(benz[*a*]anthracen-11-yl)butyric acid in 81% yield which was in turn cyclised using HF to give the ketone (**5**).

1,2,3,4-*Tetrahydrodibenz*[a,j]*anthracen-4-ol* (**6**).—2,3-Dihydrodibenz[*a,j*]anthracen-4(1*H*)-one (**5**) (2.0 g, 6.8 mmol) was dissolved in a mixture of THF (40 ml) and methanol (120 ml) and stirred with sodium borohydride (2.0 g, 53 mmol) at ambient temperature for 2 h. The work-up procedure involved concentration, extraction into chloroform, washing with water, drying ($MgSO_4$), concentration, and recrystallisation from chloroform–pentane to give the *alcohol* (**6**) (1.84 g, 91%), m.p. 194–196 °C (Found: C, 88.8, H, 6.0. $C_{22}H_{18}O$ requires C, 88.6; H, 6.1%); δ_H(250 MHz; $CDCl_3$) 1.86 (1 H, br s, OH), 2.04–2.26 (4 H, m, 2-H and 3-H), 3.23–3.65 (2 H, m, 1-H), 4.98 (1 H, br s, 4-

H), 7.59–7.94 (7 H, m, ArH), 8.33 (1 H, s, 7-H), 8.86 (1 H, d, $J_{12,13}$ 8 Hz, 13-H), and 9.34 (1 H, s, 14-H).

1,2-*Dihydrodibenz*[a,j]*anthracene* (**7**).—The alcohol (**6**) (1.14 g, 3.8 mmol) in dry benzene (250 ml) was gently heated (< 60 °C) with toluene-*p*-sulphonic acid (0.1 g) and hydroquinone (0.1 g) for 0.5 h. On cooling, water (300 ml) was added, and the organic layer was washed, dried (Na_2SO_4), concentrated, and purified by chromatography on Florosil using diethyl ether–pentane (1:9) as eluant. The *dihydroproduct* (**7**) was further purified by recrystallisation from chloroform–pentane (0.760 g, 71%), m.p. 135 °C (Found: C, 94.0; H, 5.7. $C_{22}H_{16}$ requires C, 94.25; H, 5.75%); δ_H(250 MHz; $CDCl_3$) 2.51–2.60 (2 H, m, 2-H), 3.44 (2 H, t, $J_{1,2}$ 9 Hz, 1-H), 6.11–6.18 (1 H, dt, $J_{2,3}$ 4.4 and $J_{3,4}$ 9.5 Hz, 3-H), 6.56–6.61 (1 H, dt, $J_{2,4}$ 1.87 and $J_{3,4}$ 9.5 Hz, 4-H), 7.24 (1 H, d, *J* 8.4 Hz, ArH), 7.52–7.8 (6 H, m, ArH), 8.22 (1 H, s, 7-H), 8.78 (1 H, d, $J_{12,13}$ 8 Hz, 13-H), and 9.3 (1 H, s, 14-H).

(±)-trans-3-*Bromo*-1,2,3,4-*tetrahydrodibenz*[a,j]*anthracen*-4-*yl Acetate* (**8**).—*N*-Bromoacetamide (0.711 g, 5.2 mmol) was added to a stirred solution of compound (**7**), (1.44 g, 5.2 mmol) and lithium acetate (1.44 g, 14 mmol) in THF (11 ml)–glacial acetic acid (50 ml) and stirring was continued for a further 1.5 h. The product was filtered off and washed with diethyl ether to give the *bromoacetate* (**8**) (1.55 g, 72%), m.p. 175–176 °C (from chloroform) (Found: C, 68.95; H, 4.7. $C_{24}H_{19}BrO_2$ requires C, 68.7; H, 4.6%); δ_H(250 MHz; $CDCl_3$) 2.17 (3 H, s, OCH_3), 2.48–2.70 (2 H, m, 2-H), 3.59 (2 H, t, $J_{1,2}$ 6 Hz, 1-H), 4.59–4.65 (1 H, m, 3-H), 6.35 (1 H, d, $J_{3,4}$ 4.3 Hz, 4-H), 7.34 (1 H, d, *J* 8.7 Hz, ArH), 7.60–7.92 (6 H, m, ArH), 8.32 (1 H, s, 7-H), 8.83 (1 H, d, $J_{12,13}$ 7.9 Hz, 13-H), and 9.34 (1 H, s, 14-H).

(±)-trans-3-*Bromo*-1,2,3,4-*tetrahydrodibenz*[a,j]*anthracen*-4-*ol* (**10**).—*N*-Bromoacetamide (0.282 g, 2 mmol) was added to a stirred solution of compound (**7**) (0.547 g, 2 mmol) in water (4 ml)–tetrahydrofuran (7 ml). The solution was stirred for 12 h at room temperature. Cold water was added (100 ml) and the product mixture was extracted with chloroform, dried (Na_2SO_4) and concentrated to yield the *bromohydrin* (**10**) (0.660 g, 86%), m.p. 170–171 °C (from chloroform) (Found: C, 69.75; H, 4.5. $C_{22}H_{17}BrO$ requires C, 70.0; H, 4.5%); δ_H(250 MHz; $CDCl_3$) 2.48–2.82 (2 H, m, 2-H), 3.52–3.64 (2 H, m, 1-H), 4.5–4.57 (1 H, m, 3-H), 5.13 (1 H, d, $J_{3,4}$ 5.5 Hz, 4-H), 7.6–7.98 (7 H, m, ArH), 8.35 (1 H, s, 7-H), 8.83 (1 H, d, $J_{12,13}$ 7.1 Hz, 13-H), and 9.31 (1 H, s, 14-H).

(±)-1,3-*Dibromo*-1,2,3,4-*tetrahydrodibenz*[a,j]*anthracen*-4-*yl Acetate* (**9**).—A mixture of the bromoacetate (**8**) (0.403 g, 0.96 mmol), *N*-bromosuccinimide (0.181 g, 1.02 mmol), and α,α′-azoisobutyronitrile (0.005 g) in CCl_4 (60 ml) was maintained at 75 °C for 20 min under an atmosphere of N_2. Activated charcoal was added (0.160 g) and the solution was filtered and concentrated. Trituration with diethyl ether gave the dibromoacetate (**9**) as an unstable mixture of diastereoisomers (0.391 g, 82%), m.p. 146–147 °C; δ_H(250 MHz; $CDCl_3$) 2.33 (3 H, s, CH_3), 2.91–3.28 (2 H, m, 2-H), 5.0–5.1 (1 H, m, 3-H), 6.26 (1 H, t, $J_{1,2}$ 3.14 Hz, 1-H), 6.66 (1 H, d, $J_{3,4}$ 9.64 Hz, 4-H), 7.19 (1 H, d, *J* 8.9 Hz, ArH), 7.63–7.89 (5 H, m, ArH), 7.99 (1 H, d, *J* 8.9 Hz, ArH), 8.30 (1 H, s, 7-H), 8.90 (1 H, d, $J_{12,13}$ 7.7 Hz, 13-H), and 9.47 (1 H, s, 14-H). This unstable mixture was used in the next step without attempting further purification.

3,4-*Epoxy*-3,4-*dihydrodibenz*[a,j]*anthracene* (**2**) *and Benz*-[7,8]*anthra*[2,1-b]*oxepine* (**19**).—A solution of the racemic dibromoacetate (**9**) (0.271 g, 0.055 mmol) was stirred in dry THF (20 ml) under nitrogen and sodium methoxide (0.4 g) was added at 0 °C. The mixture was stirred for 16 h at 0 °C (in darkness), diethyl ether (80 ml) was added, and the ethereal solution was washed with cold water and aqueous KOH, dried (K_2CO_3), and concentrated to yield a mixture of the arene oxide (**2**) (84%) and the oxepine (**19**) (16%). The total yield was 0.153 g (95%). Recrystallisation of the mixture of (**2**) and (**19**) from acetone at low temperature gave the pure *oxepine* (**19**) as yellow needles, m.p. 234–236 °C (Found: M^+, 294.104 62, $C_{22}H_{14}O$ requires *M*, 294.104 46); λ_{max}(THF), 290 (ε 31 4000) and 253 (15 400) nm; δ_H(250 MHz; $CDCl_3$) 5.74–5.79 (1 H, dd, $J_{3,2}$ = $J_{3,4}$ = 5.2 Hz, 3-H), 6.41 (1 H, d, $J_{4,3}$ 5.2 Hz, 4-H), 6.54–6.61 (1 H, dd, $J_{2,3}$ 5.3 and $J_{2,1}$ 11.2 Hz, 2-H), 7.6–8.02 (8 H, m, 1-H and ArH), 8.3 (1 H, s, 8-H), 8.83 (1 H, d, $J_{14,13}$ 8 Hz, 14-H), and 9.32 (1 H, s, 15-H).

Preparative HPLC separation was achieved using a Perkin-Elmer HS-3 sil column and diethyl ether (20%), triethylamine (1%), and hexane (79%) as eluant. The arene oxide (**2**) was obtained as an unstable crystalline compound, m.p. 96–98 °C (decomp.); λ_{max}(THF) 250 (ε 59 500), 256 (60 800), 262 (34 800), 295 (66 700), 307 (76 200), 343 (7 200), 354 (7 000), and 372 nm (7 200); δ_H(250 MHz; $CDCl_3$) 4.34–4.38 (1 H, dd, $J_{3,4}$ 3.8 and $J_{2,3}$ 3.7 Hz, 3-H), 4.72 (1 H, d, $J_{3,4}$ 3.8 Hz, 4-H), 6.73–6.79 (1 H, dd, $J_{2,3}$ 3.7 and $J_{1,2}$ 9.8 Hz, 2-H), 7.54–8.02 (8 H, m, 1-H and ArH), 8.33 (1 H, s, 7-H), 8.83 (1 H, d, $J_{12,13}$ 8 Hz, 13-H), and 9.55 (1 H, s, 14-H).

A mixture of the arene oxide (**2**) and the oxepine (**19**) (0.010 g, 63:35) was placed in a Pyrex NMR tube. $CDCl_3$ (0.5 ml) containing $SiMe_4$ and pentamethylbenzene (0.002 g) as reference was added. The NMR tube was maintained at ambient temperature by use of a cooled Pyrex glass water jacket. The sample was irradiated using a medium pressure UV lamp (Hanovia Reading Photochemical Reactor, > 300 nm) for 0.5 h. ^1H NMR analysis indicated that 67% of the original arene oxide (**2**) had been photoisomerised to the oxepine (**19**) while 43% decomposed to phenol(s).

(−)-(3R,4R) *and* (+)-(3S,4S)-trans-3-*Bromo*-1,2,3,4-*tetrahydrodibenz*[a,j]*anthracen*-4-*yl* 3,3,3-*Trifluoro*-2-*methoxy*-2-*phenylpropionate* (**11b** *and* **11a**).—(−)-MTPA chloride (1.58 g, 6.3 mmol) [obtained from (−)-MTPA] was added to a stirred solution of the racemic bromohydrin (**13**) (1.96 g, 5.2 mmol), *p*-dimethylaminopyridine (0.006 g, 0.05 mmol), and dry pyridine (5 ml) at 0 °C and stirring was continued for 24 h. Water (30 ml) was added and the precipitated product was extracted into diethyl ether. The latter solution was washed with water, dried (Na_2SO_4), and concentrated to yield a diastereoisomeric mixture of bromo-MTPA esters (**11a**/**11b**). A partial separation of diastereoisomers (**11a**/**11b**) was achieved by short-column chromatography on silica gel using diethyl ether–pentane (5:95) as eluant. Fractional crystallisation from diethyl ether yielded pure samples of each *diastereoisomer*: (3*R*,4*R*)-(**11b**): high R_f, less polar isomer (1.03 g, 33%), m.p. 170–171 °C (Found: C, 64.8; H, 4.1 $C_{32}H_{24}BrF_3O_3$ requires C, 64.8; H, 4.1%), $[\alpha]_D$ −99° ($CHCl_3$), δ_F(94.18 MHz; $CDCl_3$) −8.62 ppm (3 F, s, CF_3); δ_H(250 MHz; $CDCl_3$), 2.44 (2 H, m, 2-H), 3.54 (3 H, s, OMe), 3.58 (2 H, m, 1-H), 4.60 (1 H, m, 3-H), 6.5 (1 H, d, $J_{3,4}$ 3.65 Hz, 4-H), 7.26–7.95 (12 H, m, ArH), 8.35 (1 H, s, 7-H), 8.83 (1 H, d, $J_{12,13}$ 7.9 Hz, 13-H), and 9.36 (1 H, s, 14-H). (3*S*,4*S*)-(**11a**): low R_f, more polar isomer (0.93 g, 31%), m.p. 168–169 °C (Found: C, 65.0; H, 3.9%); $[\alpha]_D$ +68° ($CHCl_3$); δ_F(94.18 MHz; $CDCl_3$) −8.66 ppm (3 F, s, CF_3); δ_H(250 MHz; $CDCl_3$) 2.54–2.64 (2 H, m, 2-H), 3.56–3.62 (5 H, m and s, 1-H and OCH_3), 4.68 (1 H, m, 3-H), 6.56 (1 H, d, $J_{3,4}$ 4.14 Hz, 4-H), 7.18–7.88 (12 H, m, ArH), 8.3 (1 H, s, 7-H), 8.83 (1 H, d, $J_{12,13}$ 7.8 Hz, 13-H), and 9.3 (1 H, m, 14-H).

(+)-(3R,4R) *and* (−)-(3S,4S)-trans-3-*Bromo*-1,2,3,4-*tetrahydrodibenz*[a,j]*anthracen*-4-*ol* (**10**).—The bromo MTPA diastereoisomer (−)-(**11b**) (0.248 g, 0.4 mmol; $[\alpha]_D$ −99°) was dissolved in diethyl ether (30 ml) and the solution was cooled to

0 °C. A solution of di-isobutylaluminium hydride (Dibal-H) under nitrogen (6 ml; 1M solution in hexane) was added to the stirred solution and the reaction was terminated after 12 h by addition of methanol (10 ml) and pentane (2 ml) followed by dropwise addition of dilute sulphuric acid (50 ml). The organic layer was washed with water, dried (Na_2SO_4), concentrated, and purified by flash column chromatography on Florisil using diethyl ether–pentane (1:9) as eluant to yield the (+)-(3*R*,4*R*)-bromohydrin (**10**) (0.115 g, 74%), m.p. 179–180 °C (from chloroform–pentane), $[\alpha]_D$ +94° ($CHCl_3$).

Similar treatment of the bromo-MTPA diastereoisomer (+)-(**11a**) (0.328 g, 0.6 mmol; $[\alpha]_D$ +68°) yielded the (−)-(3*S*,4*S*)-bromohydrin (**10**) (0.170 g, 82%), m.p. 179–180 °C, $[\alpha]_D$ −94° ($CHCl_3$). The (+)- and (−)-enantiomers of the bromohydrin (**10**) were spectrally indistinguishable from the racemic sample.

(−)-(3R,4R)-trans-3-*Bromo*-1,2,3,4-*tetrahydrodibenz*[a,j]-*anthracen*-4-*yl Acetate* (**8**).—The (+)-bromohydrin (**10**) (0.082 g, 0.22 mmol; $[\alpha]_D$ +94°) was stirred with acetic anhydride (1.5 ml) and *p*-dimethylaminopyridine (0..002 g, 0.02 mmol) in pyridine (2 ml) at 0 °C for 2 h. Water was added (20 ml) and the product was extracted into diethyl ether. The latter solution was washed with water and dilute HCl, dried (Na_2SO_4), concentrated, and chromatographed on Florisil using diethyl ether–pentane as eluant to yield the bromoacetate (**8**) (0.064 g, 70%), m.p. 169–170 °C (from chloroform–pentane), $[\alpha]_D$ −77° ($CHCl_3$). This product gave spectral data identical with those of the racemic sample.

(−)-(3R,4R)-1,3-*Dibromo*-1,2,3,4-*tetrahydrodibenz*[a,j]-*anthracen*-4-*yl Acetate* (**9**).—Using an identical procedure to that discussed for the racemic sample, the (−)-bromoacetate (**8**) (0.057 g, 0.14 mmol; $[\alpha]_D$ −77°) was treated with *N*-bromosuccinimide in carbon tetrachloride to yield a mixture of dibromoacetate diastereoisomers (**9**) (0.035 g, 52%), m.p. 128–129 °C, $[\alpha]_D$ −514° ($CHCl_3$) with identical spectra to those of the racemic sample.

3,4-*Epoxy*-3,4-*dihydrobenz*[a,j]*anthracene* (**2**) *and* (**19**).—Treatment of the (−)-dibromoacetate mixture (**9**) (0.035 g, 0.007 mmol; $[\alpha]_D$ −514°) with NaOMe in dry THF as reported for the racemic sample yielded a mixture of the arene oxide (**2**) and the oxepine (**19**) (0.013 g, 65%) in the ratio of 65:35 which gave an $[\alpha]_D$ value of 0° ($CHCl_3$). This value did not change in measurements of optical rotations at lower wavelengths.

(−)-(3R,4S)-3,4-*Epoxy*-1,2,3,4-*tetrahydrodibenz*[a,j]-*anthracene* (**12**).—A mixture of the bromohydrin (**10**) (0.165 g, 0.44 mmol; $[\alpha]_D$ −94°) and the basic form of Amberlite resin (IRA-900; 2.5 g) was stirred in dry THF (30 ml) at room temperature for 2 h. The mixture was filtered and the filtrate concentrated and triturated with diethyl ether to give the *epoxide* (**12**) (0.125 g, 96%), m.p. 155–157 °C, $[\alpha]_D$ −88° ($CHCl_3$) (Found: M^+, 296.120 05. $C_{22}H_{16}O$ requires *M*, 296.120 11), δ_H(250 MHz; $CDCl_3$) 1.92–2.0 (1 H, m, 2-H), 2.7–2.74 (1 H, m, 2-H), 2.97 (1 H, m, 1-H), 3.65–3.74 (1 H, m, 1-H), 3.88 (1 H, m, 3-H), 4.02 (1 H, d, $J_{4,3}$ 4.2 Hz, 4-H), 7.54–7.91 (7 H, m, ArH), 8.3 (1 H, s, 7-H), 8.8 (1 H, d, $J_{12,13}$ 7.98 Hz, 13-H), and 9.34 (1 H, s, 14-H).

(+)-(3R,4S)-cis- *and* (−)-(3R,4R)-trans-1,2,3,4-*Tetrahydrodibenz*[a,j]*anthracen*-3,4-*diol* (**17**) *and* (**13**).—To a mixture of dioxane (40 ml)–water (100 ml) which had been previously adjusted to pH 2.5 by addition of perchloric acid (60%; 2 drops) and buffered with sodium perchlorate (0.1M; 5 ml) was added a solution of the tetrahydroepoxide (**12**) (0.125 g, 0.42 mmol; $[\alpha]_D$ −88°) in dioxane (5 ml). The reaction mixture was stirred for 0.5 h after which time it was neutralised ($NaHCO_3$) and concentrated under reduced pressure and the residue was extracted into ethyl acetate. The latter solution was dried (Na_2SO_4), concentrated, and purified using preparative TLC and methanol–chloroform (5:95) as eluant to yield the *cis*- (**17**) and *trans*- (**13**) diols: (+)-(3R,4S)-cis-*diol* (**17**) (0.018 g, 14%), m.p. 260–262 (from EtOAc); $[\alpha]_D$ +173° (THF) (Found: M^+, 314.130 84, $C_{22}H_{18}O_2$requires *M*, 314.130 67); δ_H[400 MHz; $(CD_3)_2CO$] 1.9–2.2 (1 H, m, 2-H), 2.2–2.34 (1 H, m, 2-H), 3.3–3.4 (1 H, m, 1-H), 3.66–3.73 (1 H, m, 1-H), 4.09–4.12 (1 H, m, 3-H), 4.80 (1 H, d, $J_{3,4}$ 3.6 Hz, 4-H), 7.63–7.76 (7 H, m, ArH), 8.46 (1 H, s, 7-H), 9.05 (1 H, d, $J_{12,13}$ 8.1 Hz, 13-H), and 9.5 (1 H, s, 14-H); (−)-(3R,4R)-trans-*diol* (**13**) (0.050 g, 38%), m.p. 241–242 °C (from EtOAc); $[\alpha]_D$ −31° (THF) (Found: M^+, 314.130 84); δ_H[400 MHz; $(CD_3)_2CO$], 2.09–2.12 (1 H, m, 2-H), 2.34–2.40 (1 H, m, 2-H), 3.41–3.49 (1 H, m, 1-H), 3.6–3.68 (1 H, m, 1-H), 3.95–4.1 (1 H, m, 3-H), 4.67 (1 H, d, $J_{3,4}$ 6.4 Hz, 4-H), 7.63–7.77 (7 H, m, ArH), 8.45 (1 H, s, 7-H), 9.04 (1 H, d, $J_{12,13}$ 8.2 Hz, 13-H), and 9.46 (1 H, s, 14-H).

(−)-(3R,4R)-trans-1,2,3,4-*Tetrahydrodibenz*[a,j]*anthracen*-3,4-*diyl Diacetate* (**14**).—The *trans*-diol (**3**) (0.046 g, 0.15 mmol; $[\alpha]_D$ −31°) was stirred for 0.5 h with acetic anhydride (1 ml) in dry pyridine (15 ml) containing *p*-dimethylaminopyridine (0.002 g, 0.02 mmol). Water was added (20 ml) and the crude product was extracted into diethyl ether. The latter solution was washed in turn with water, dilute HCl, and water again prior to drying (Na_2SO_4) and concentration. Column chromatography using Florosil and diethyl ether–pentane (2:8) as eluant yielded the *trans*-diacetate (**14**) (0.036 g, 62%), m.p. 243–245 °C; $[\alpha]_D$ −146° ($CHCl_3$) (Found: M^+, 398.152 38. $C_{26}H_{22}O_4$ requires *M*, 398.152 46); δ_H(250 MHz; $CDCl_3$) 2.07 (3 H, s, OMe), 2.17 (3 H, s, OMe), 2.31–2.44 (2 H, m, 2-H), 3.53 (2 H, t, $J_{1,2}$ 5.94 Hz, 1-H), 5.30–5.37 (1 H, m, 3-H), 6.26 (1 H, d, $J_{3,4}$ 5.34 Hz, 4-H), 7.27–7.93 (7 H, m, ArH), 8.33 (1 H, m, 7-H), 8.83 (1 H, d, $J_{12,13}$ 8 Hz, 13-H), and 9.3 (1 H, s, 14-H).

(−)-(3R,4R)-trans-1-*Bromo*-1,2,3,4-*tetrahydrodibenz*[a,j]-*anthracen*-3,4-*diyl Diacetate* (**15**).—Benzylic bromination of the diacetate (**14**) (0.034 g, 0.085 mmol; $[\alpha]_D$ −146°) was carried out under similar conditions to those used in the synthesis of the dibromoacetate (**9**). Thus, using *N*-bromosuccinimide (0.016 g, 0.089 mmol) in CCl_4 (8 ml), a mixture of bromodiacetate isomers (**15**) (0.035 g, 85%), m.p. 141–143 °C; $[\alpha]_D$ −343° ($CDCl_3$) was obtained. Attempted separation and purification of the isomers resulted in decomposition so the mixture was utilised in the next stage without further purification: diacetate (**15**) (major isomer), δ_H(250 MHz; $CDCl_3$) 2.15 (3 H, s, OMe), 2.25 (3 H, s, OMe), 2.5–2.7 (1 H, m, 2-H), 2.8–2.97 (1 H, m, 2-H), 5.89–6.05 (1 H, m, 3-H), 6.32–6.35 (1 H, m, 1-H), 6.54 (1 H, d, $J_{3,4}$ 8.5 Hz, 4-H), 7.33–8.09 (7 H, m, ArH), 8.36 (1 H, s, 7-H), 8.91 (1 H, d, $J_{12,13}$ 7.6 Hz, 13-H), and 9.51 (1 H, s, 14-H); (**15**), (minor isomer) δ_H(250 MHz; $CDCl_3$) 2.11 (3 H, s, OMe), 2.12 (3 H, s, OMe), 2.5–2.7 (1 H, m, 2-H), 2.8–2.97 (1 H, m, 2-H), 5.23–5.31 (1 H, m, 3-H), 6.23–6.24 (1 H, m, 1-H), 6.54 (1 H, d, $J_{3,4}$ 8.5 Hz, 4-H), 7.33–8.09 (7 H, m, ArH), 8.38 (1 H, s, 7-H), 8.92 (1 H, d, $J_{12,13}$, 7.6 Hz, 13-H), and 9.65 (1 H, s, 14-H).

(−)-(3R,4R)-trans-3,4-*Dihydrodibenz*[a,j]*anthracen*-3,4-*diyl Diacetate* (**16**).—To a solution of the bromodiacetate (**15**) (0.035 g, 0.074 mmol; $[\alpha]_D$ −343°) in dry THF (2 ml) at 0 °C under N_2 was added 1,5-diazabicyclo[4.3.0]non-5-ene (0.285 g, 2.5 mmol). The mixture was stirred for 16 h at room temperature and the product was extracted into ethyl acetate (50 ml), washed with water, dilute HCl, and sodium hydrogen carbonate solution, dried (Na_2SO_4), and concentrated to yield the dihydrodiacetate (**16**) (0.008 g, 28%), m.p. 130 °C (decomp.); $[\alpha]_D$ −165° ($CHCl_3$) δ_H(250 MHz; $CDCl_3$), 2.01 (3 H, s, OMe), 2.08 (3 H, s, OMe). 5.62 (1 H, dd, $J_{3,4} = J_{2,3}$ = 5.0 Hz, 3-H), 6.31 (1 H, d, $J_{3,4}$ 5.0 Hz, 4-H), 6.27–6.31 (1 H, m, 2-H), 6.93–7.95

(8 H, m, 1-H and ArH), 8.29 (1 H, s, 7-H), 8.79 (1 H, d, $J_{12,13}$ 7.5 Hz, 13-H), and 9.43 (1 H, s, ArH).

(−)-(3R,4R)-trans-3,4-*Dihydrodibenz*[a,j]*anthracen*-3,4-*diol* (**3**).—The dihydro-diacetate (**16**) (0.008 g, 0.02 mmol; $[\alpha]_D$ −165°) was dissolved in dry THF (2 ml) and dry methanol (2 ml) and ammonia was bubbled through the solution for 0.25 h at 0 °C. The mixture was then stirred for 18 h at room temperature, concentrated, and purified by column chromatography on Florisil. Elution with dichloromethane–ethyl acetate (1:1) yielded the product *dihydro-diol* (**3**) (0.0035 g, 58%), m.p. 222–224 °C (from CH_2Cl_2); $[\alpha]_D$ −194° (THF) (Found: M^+, 312.115 13. $C_{22}H_{16}O_2$ requires M, 312.115 02); δ_H(400 MHz; $CDCl_3$) 4.52–4.66 (1 H, dd, $J_{3,4}$ 11.6 and $J_{2,3}$, 2.3 Hz, 3-H), 4.96 (1 H, d, $J_{3,4}$ 11.6 Hz, 4-H), 6.17–6.23 (1 H, dd, $J_{2,3}$ 2.3 and $J_{1,2}$ 10.2 Hz, 2-H), 7.49–7.97 (8 H, m, 1-H and ArH), 8.36 (1 H, s, 7-H), 8.98 (1 H, d, $J_{12,13}$ 8.1 Hz, 13-H), and 9.53 (1 H, s, 14-H).

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