



# Chemical and Enzyme-Catalysed Synthesis of Quinoline Arene Hydrates

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**Abstract**—Arene hydrates of quinoline have been synthesized by enzyme-catalysed benzylic and allylic hydroxylation of dihydroquinolines in growing cultures of the fungus *Mortierella isabellina* and in liver microsomal preparations. A preference for allylic hydroxylation was generally observed in eukaryotic systems. Evidence of epoxidation of dihydroarenes by both the fungal and animal enzyme systems was also obtained. The chemical synthesis of these arene hydrates (5-hydroxy-5,6-dihydroquinoline, 6-hydroxy-5,6-dihydroquinoline, 7-hydroxy-7,8-dihydroquinoline, and 8-hydroxy-7,8-dihydroquinoline) from the corresponding hydroxy-5,6,7,8-tetrahydroquinolines, has also been accomplished.

## Introduction

The first reported synthesis of an arene hydrate, an adduct formed by addition of one molecule of water to an arene, appeared about 100 years ago.<sup>1</sup> Thus, early studies on the metabolism of naphthalene,<sup>2-6</sup> anthracene,<sup>4,7</sup> phenanthrene<sup>4</sup>, and quinoline<sup>8,9</sup> were considered to be consistent with the formation of unstable arene hydrate intermediates. More recent studies have shown that cyclopenta[*c,d*]pyrene can be biotransformed to an arene hydrate using liver microsomal systems.<sup>10</sup> Acetophenone has also been reported to yield an arene hydrate metabolite in the presence of growing cultures of the bacterium *Pseudomonas putida* UV4.<sup>11</sup>

Monohydroxylation of dihydroarenes catalysed by mammalian liver enzymes was previously reported to yield arene hydrates of naphthalene<sup>6</sup> and benz(e)pyrene<sup>12</sup> of unspecified structure. Arene hydrates of naphthalene have, however, recently been isolated and unequivocally identified using animal liver microsomes and pure enzymes,<sup>13</sup> and bacterial, *P. putida* UV4,<sup>14,15</sup> systems. Both structure and absolute stereochemistry were assigned to these arene hydrates.<sup>13-15</sup> Prior to the present report, arene hydrates do not appear to have been detected in, or isolated from, fungi.

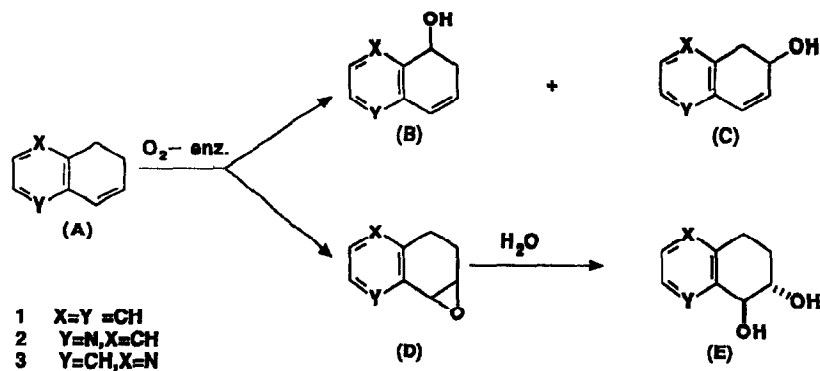
The isolation and characterization of naphthalene arene hydrates<sup>14,15</sup> and their chemical synthesis<sup>15</sup> was initially hampered by their fast rate of aromatization under acidic conditions.<sup>16</sup> Based upon past experience of the greater stability of the arene oxide metabolites of quinoline, with respect to aromatization, compared with naphthalene oxides<sup>17-19</sup>, it was postulated that the arene hydrate derivatives of quinoline might also be much more stable and thus more readily detected and isolated, than their carbocyclic analogues. Quinoline should thus be considered as a suitable substrate in the quest for arene hydrate formation from fungal systems. The detection of arene

hydrates of quinoline as both fungal and liver enzyme metabolites, and unequivocal confirmation of their structures by chemical synthesis, is now reported.

## Results and Discussion

The enzyme-catalysed synthesis of the naphthalene arene hydrates **1B** and **1C** from 1,2-dihydronaphthalene **1A** has been achieved in both eukaryotic (mammalian liver enzymes)<sup>13</sup> and prokaryotic systems (*P. putida* UV4).<sup>14,15</sup> Metabolism of 1,2-dihydronaphthalene (**1A**), using intact cells of the fungus *Mortierella isabellina* during the present studies, did not however appear to yield the expected arene hydrates **1B** and **1C** but gave only the *trans*-diol **1E** with a preference for the [1*R*,2*R*] enantiomer (34% *e.e.*). This result is consistent with enzyme-catalysed epoxidation of 1,2-dihydronaphthalene (**1A**) to yield the tetrahydroepoxide **1D** followed by chemical or enzyme-catalysed hydrolysis of the epoxide to give the *trans*-diol **1E** (Scheme I). While both of the eukaryotic systems studied, i.e. liver microsomes<sup>13</sup> and fungi, produced the *trans*-diol **1E** as a major metabolite, only the former showed evidence of arene hydrate formation. The longer incubation times used during fungal biotransformations may however have allowed decomposition of naphthalene arene hydrates **1B** and **1C** to occur.

In view of the unexpected oxidation of alkene **1A** in *M. isabellina* to yield the *trans*-diol **1E** as the major metabolite, without evidence of benzylic hydroxylation, the possibility of a similar reaction occurring with other bicyclic alkenes was also investigated. Thus, a similar oxidation pathway was observed when indene and 1,2-dihydrophenanthrene were added to *M. isabellina* cultures. The corresponding *trans*-diols (**4** and **5**) were isolated as metabolites with similar yields (32-34 %) but opposite stereochemistry, i.e. (1*R*,2*R* ; 41 % *e.e.*) and (3*S*,4*S* ; 15 %



Scheme I.

Table 1. Relative yields of metabolites of dihydroquinoline from  $^1\text{H-NMR}$  and GC-MS data

Substrate	Enzyme System	Products <sup>a</sup>	Total Isolated Yield
2A	<i>M. isabellina</i>	2B(11%) 2C(46%) 2D(43%)	28%
3A	<i>M. isabellina</i>	3B(<1%) 3C(58%) 3D(42%)	24%
2A	PB microsomes <sup>b</sup>	2B(32%) 2C(68%) 2D(<1%)	ca. 2%
2A	3MC microsomes <sup>c</sup>	2B(72%) 2C(28%) 2D(<1%)	ca. 2%
3A	PB microsomes <sup>b</sup>	3B <sup>d</sup> , 3C <sup>d</sup> , 3D <sup>d</sup>	<2%
3A	3MC micromes <sup>c</sup>	3B <sup>d</sup> , 3C <sup>d</sup> , 3D <sup>d</sup>	<2%

a. Yields of *trans*-dihydrodiols (2E, 3E) were <1 % in all cases.

b. Phenobarbital-induced rats used.

c. 3-Methylcholanthrene-induced rats used.

d. Insufficient material present for quantitation.

*e.e.*), respectively. Holland *et al.* have also observed *trans*-diol metabolites during biotransformation of alkenes including that of compound 1A and a range of acyclic alkenes by *M. isabellina*.<sup>20</sup> It is noteworthy that in all cases these bicyclic alkenes were preferentially oxidized and subsequently hydrated to yield *trans*-diols, without evidence of benzylic hydroxylation and that the yield and stereochemistry of these *trans*-diol metabolites were all similar.

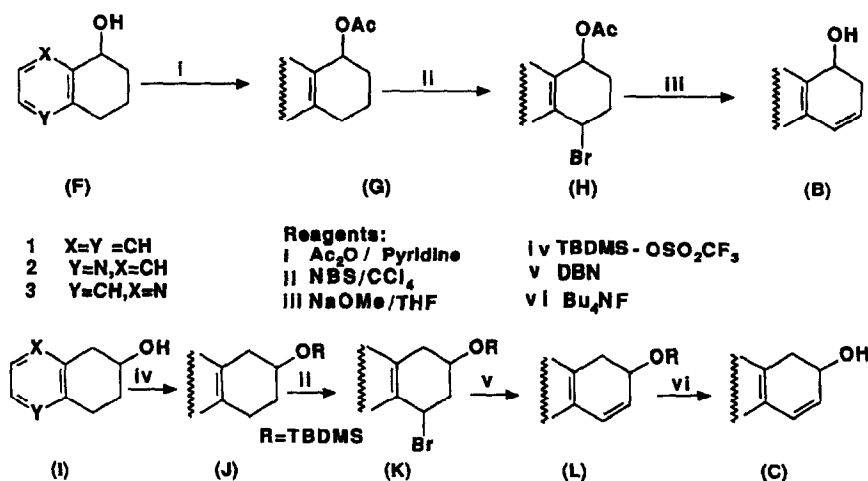
Metabolism of 5,6- (2A) and 7,8-dihydroquinoline (3A) using intact cells of *M. isabellina* did not produce the expected corresponding *trans*-diols 2E and 3E but yielded instead the tetrahydroepoxides 2D (12 % yield) and 3D (10 % yield) in racemic forms (Table 1). The stability of the latter epoxides to acid-catalysed hydration, compared with the epoxide 1D, may have been a significant factor in their detection. Surprisingly, the major metabolites isolated from 5,6-dihydroquinoline (2A) appeared, on the basis of  $^1\text{H-NMR}$  analysis, to be a mixture of the arene hydrates of quinoline (2B and 2C). Attempts to separate this mixture by TLC and HPLC methods were unsuccessful. The mixture of isomers 2B and 2C, in 16 % isolated yield, was only found to be separable by GC-MS analysis. Unequivocal identification of compounds 2B and 2C was achieved by  $^1\text{H NMR}$  and mass spectral comparison with authentic samples obtained by chemical synthesis (Scheme II). Although the isomeric mixture 2B and 2C was optically active ( $[\alpha]_D -31^\circ$  [ $\text{CHCl}_3$ ]), neither absolute

configurations nor enantiomeric excess values were determined. The major arene hydrate metabolite 2C resulted from allylic hydroxylation.

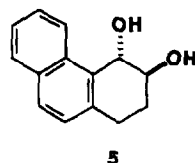
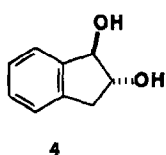
A pure sample of arene hydrate 3C was isolated in 14 % yield from metabolism of 7,8-dihydroquinoline 3A. It was found to be optically active ( $[\alpha]_D -18^\circ$  [ $\text{CHCl}_3$ ]) and of low enantiopurity (18 % *e.e.*) by chiral stationary phase HPLC analysis. No evidence for the isomeric arene hydrate 3B was found, again indicating a preference for the allylic hydroxylation.

In an extension of earlier studies from these laboratories on arene hydrate formation during liver enzyme metabolism of 1,2-dihydronaphthalene (1A)<sup>13</sup> and the possible involvement of arene hydrates during the metabolism of quinoline by animals,<sup>8,9,18,19</sup> a preliminary investigation of the metabolism of 5,6-dihydro- (2A) and 7,8-dihydroquinoline (3A) by liver microsomal fractions was undertaken.

The dihydroquinolines 2A and 3A proved to be poor substrates for the enzymes present in rat liver microsomal fractions. Thus, while earlier work with 1,2-dihydronaphthalene (1A)<sup>13</sup> showed the substrate to be largely metabolized (> 90 %), 5,6-dihydroquinoline (2A) (ca 2 % metabolism) and 7,8-dihydroquinoline (3A) (< 2 % metabolism) were very poorly biotransformed to give much lower yields of extractable metabolites under similar



Scheme II.



conditions. The possibility of quaternary salt formation of either substrate (2A or 3A) or products from protonation of the nitrogen atom may have contributed to the poor yields of the expected metabolites.

Despite the low yields of biotransformation products from the dihydroquinolines 2A and 3A, GC-MS analysis of the trimethylsilyl ether derivatives allowed the arene hydrates of quinoline, resulting from benzylic (2B,3B) and allylic hydroxylation (2C,3C), to be separated and detected. Traces of the corresponding tetrahydroepoxides 2D and 3D and the *trans* diol 2E were also present among the metabolites detected by the use of sensitive GC-MS methods, e.g. the SIM mode.

Previous results<sup>13</sup> appear to indicate that hydroxylation occurs to give more of the arene hydrate 1C, bearing an allylic hydroxyl group, than the benzylic hydroxylation product, 1B, when 1,2-dihydronaphthalene (1A) was oxidized by liver enzymes from either phenobarbital (PB)- or 3-methylcholanthrene (3-MC)-induced microsomes.

Although <sup>18</sup>O-labelling studies have not been carried out in the present work, it is probable that the oxygen atoms, introduced at either the benzylic and allylic positions during the liver microsomal oxidations, are derived from aerial dioxygen. The atmospheric origin of the oxygen atom has recently been established in the formation of arene hydrates 1B and 1C from 1,2-dihydronaphthalene (1A) with liver enzymes.<sup>13</sup>

The arene hydrates, having an allylic hydroxyl group, appear to be the main extractable metabolites in both fungal (*M. isabellina*, 2C, 3C) and animal (PB- induced liver enzymes, 1C, 2C) studies.<sup>19</sup> An exception was found while using 3-MC-induced liver enzymes where arene hydrate 2B was the major hydrate. This general preference

for allylic hydroxylation contrasts with bacterial (*P. putida* UV4) metabolism where benzylic hydroxylation of alkene 1A gave only arene hydrate 1B. Neither the dihydroquinoline substrate 2A nor 3A was metabolized by the latter bacterial system. Since arene hydrates 2B, 2C, 3B and 3C appeared to be formed as metabolites in eukaryotic systems, unequivocal confirmation, by comparison with chemically synthesized samples, was required.

The chemical synthesis of the arene hydrates 2B, 3B, 2C and 3C was carried out in a similar manner to that previously reported<sup>15</sup> for arene hydrates 1B and 1C (Scheme II). The benzylic alcohol precursors 2F and 3F were available from earlier studies.<sup>19</sup> The non-benzylic alcohols 2I and 3I were readily obtained by catalytic hydrogenation of the corresponding available epoxides.<sup>19</sup> The reagents used, during the chemical synthesis of the four arene hydrates 2B, 3B, 2C and 3C, are shown in Scheme II. The synthetic steps involved were based upon well established reactions. The intermediates 2K and 3K, proved to be unstable mixtures of isomers. These could only be identified by spectral methods and were immediately used in the next step without further purification. All of the arene hydrates 2B, 2C, 3B and 3C, were found to be much more stable towards acid-catalysed dehydration compared with their carbocyclic analogues,<sup>16</sup> as was anticipated from earlier studies on the aromatization of quinoline arene oxides.<sup>17-19</sup> The hydrates 2B, 2C, 3B and 3C could thus be purified by preparative TLC on silica gel and recrystallization. While they showed resistance to acid-catalysed dehydration, they did however undergo slow oxidation in air and became darker in colour upon normal storage at ambient temperature. In past studies, involving the metabolism of quinoline by liver microsomal enzymes, we were able to detect an arene oxide intermediate directly, i.e. quinoline 5,6-oxide.<sup>18,19</sup> No

evidence was found in that study, however, for the presence of the arene hydrates of quinoline. Although authentic samples of quinoline arene hydrates were unavailable for comparison purposes, at the time of that work,<sup>18</sup> it is clear that these would have been both sufficiently stable and readily detectable had they been present.

### Conclusion

Four possible arene hydrates of quinoline (**2B**, **3B**, **2C** and **3C**) have been synthesized by chemical methods and have proved to be relatively stable compounds in comparison with their carbocyclic analogues. Fungal oxidation (*M. isabellina*) of bicyclic alkenes was generally found to favour epoxidation followed by hydrolysis to yield *trans*-tetrahydriols without benzylic or allylic hydroxylations. The epoxide metabolites of 5,6- and 7,8-dihydroquinolines, **3D** and **2D**, were detected and isolated in racemic form. The arene hydrates of quinoline **2B**, **2C** and **3C** were also detected as fungal hydroxylation metabolites.

Although none of the arene hydrates **2B**, **2C**, **3B** and **3C** were detected when quinoline was metabolized by liver microsomal fractions, they have now all been detected as metabolites of both 5,6- and 7,8-dihydroquinolines using the same enzyme system. The arene hydrates of quinoline proved to be sufficiently stable and thus detectable as metabolites in eukaryotic systems.

### Experimental

Mps and bps were uncorrected. <sup>1</sup>H NMR spectra were recorded at 250 MHz (Bruker WM250) and 300 MHz (General Electric QE 300) with CDCl<sub>3</sub> as solvent. Flash chromatography and preparative TLC were carried out using Merck Kieselgel 60 (250–400 mesh) and Merck Kieselgel PF<sub>254</sub> and PF<sub>366</sub> respectively. Reversed phase TLC was performed on Whatman KC<sub>18</sub>F plates. GC-MS analyses were obtained on a VG12-250 instrument (25 m BP1 column) linked to a PDP11/23 PLUS data system or a Hewlett-Packard GC-5890 (HP-ULTRA-1 column) linked to a MSD-5970 detector. Optical rotations were determined, at ambient temperature, on a Perkin-Elmer automatic precision polarimeter Model 241 at the sodium-D line 589 nm. Accurate molecular masses were determined by the peak-matching method using perfluorokerosene as standard reference.

The preparation of liver microsomes and microsomal incubations were carried out as described in a recent publication.<sup>13</sup> Biotransformations using the fungus *Mortierella isabellina* were conducted, employing a shake culture technique, following the procedure described in an earlier report.<sup>21</sup> <sup>1</sup>H NMR spectra of the crude extracts and GC-MS data, obtained after solvent extraction of the aqueous biotransformed material, were routinely recorded before any purification.

### Analysis of phenobarbital (PB)- and 3-methylcholanthrene(3-MC)-induced microsomal and fungal metabolites by GC-MS

The aqueous biotransformed material was saturated with sodium chloride and then extracted with ethyl acetate. The extract was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under nitrogen. A portion of the residue was silylated with bis(trimethylsilyl)trifluoroacetamide in pyridine. GC-MS analysis of the silylated mixture was performed using an HP-ULTRA-1 column at 80 °C (hold 2 min, ramp 10 °C min<sup>-1</sup>) to 200 °C (ramp 25 °C min<sup>-1</sup>) to 300 °C in normal or SIM mode. Standard samples of 5-hydroxy-5,6-dihydroquinoline (**2B**), 6-hydroxy-5,6-dihydroquinoline (**2C**), 7-hydroxy-7,8-dihydroquinoline (**3B**) and 8-hydroxy-7,8-dihydroquinoline (**3C**) were chemically synthesized for comparison purposes (see later).

The GC-MS data for 5,6-dihydroquinoline (**2A**) metabolites (PB and 3-MC) showed prominent peaks at 8.62 and 8.70 min, which corresponded to the retention times of arene hydrates (**2B**) and (**2C**) respectively. The mass spectrum corresponding to each peak was indistinguishable from that of an authentic sample of arene hydrate (**2B**, **2C**). The GC-Mass spectrum also contained minor peaks at retention times 7.37 and 10.08 min. The peak at 7.37 min and the corresponding mass spectrum (SIM mode) were identical to those of an authentic sample of epoxide **3D**.<sup>19</sup> Similarly the GC-MS data of the later eluting compound (10.08 min) were found to be identical with a reference sample of *trans*-diol **3E**.<sup>19</sup> The GC-MS data from 7,8-dihydroquinoline (**3A**) metabolites (trimethylsilyl derivatives) exhibited peaks at retention time 8.45, 9.45 and 7.32 min. The peaks were identified as arene hydrates **3B** (8.45 min) and **3C** (9.45 min) and the epoxide **3D** (7.32 min) by direct comparison (GC-MS data) with standard samples.

GC-MS analysis was similarly used to separate and identify the isomeric arene hydrates **2B** and **2C** formed by fungal metabolism (*M. isabellina*).

### Enzyme catalysed synthesis of *trans*-diol metabolites in *Mortierella isabellina*

Biotransformation of the bicyclic alkenes, indene, 1,2-dihydronaphthalene and 1,2-dihydrophenanthrene (*ca* 100 mg each), was carried out using intact cultures of *M. isabellina*. The dichloromethane extract of the aqueous culture medium, containing the biotransformed products, was concentrated and purified by preparative TLC (dichloromethane–methanol 19:1). The optical purity of each *trans*-diol was determined by comparison of the [α]<sub>D</sub> value with the literature value and also by <sup>1</sup>H NMR spectral analysis of the di-MTPA ester derivatives. (–)-(1*R*,2*R*)-*trans*-indan-1,2-diol (**4**). Yield, 44 mg (34 %); [α]<sub>D</sub> –12 ° (*c* = 0.25, EtOH); *e.e.* 40 %. (+)-(1*R*,2*R*)-*trans*-1,2-dihydroxy-1,2,3,4-tetrahydronaphthalene (**1E**). Yield, 22 mg (17 %); [α]<sub>D</sub> +38 ° (*c* = 0.18, CHCl<sub>3</sub>); *e.e.* (34 %). (–)-(3*S*,4*S*)-*trans*-3,4-Dihydroxy-1,2,3,4-tetrahydrophenanthrene (**5**). Yield, 20 mg (17 %); [α]<sub>D</sub> –4.6 ° (*c* = 0.8; CHCl<sub>3</sub>); *e.e.* 15 %.

*Enzyme catalysed synthesis of arene hydrates 2B, 2C, 3C and epoxides 2D and 3D in M. isabellina*

Bioconversion of 5,6-dihydroquinoline (2A) and 7,8-dihydroquinoline (3A) (100 mg each) was in turn carried out with *M. isabellina*. The isolated metabolites were identified by spectral ( $^1\text{H}$  NMR and GC-MS) comparisons with the standard samples.

*5-Hydroxy-5,6-dihydroquinoline (2B) and 6-hydroxy-5,6-dihydroquinoline (2C)*

These two metabolites of 5,6-dihydroquinoline (2A) could not be separated by liquid chromatographic methods and as such were identified as components of a mixture; (17 mg, 15 %),  $[\alpha]_{\text{D}} -31^\circ$  ( $c = 0.4$ ,  $\text{CHCl}_3$ ). The relative amount of 5-hydroxy compound 2B to 6-hydroxy compound 2C was estimated to be 16:84 by  $^1\text{H}$  NMR spectral and GC-MS analyses.

*7,8-Epoxy-5,6,7,8-tetrahydroquinoline (2D)*

The epoxide 2D was separated from the unmetabolized substrate 2A by reversed phase TLC (methanol–water, 4:1), yield 13 mg (12 %), as an oil which was found to be racemic. Chiral stationary phase HPLC showed separation of its enantiomers ( $\alpha$  1.20) (Chiracel OB column 25 cm  $\times$  4.6 mm; 20 % propan-2-ol/hexane, 0.5 mL  $\text{min}^{-1}$ ).

*7-Hydroxy-7,8-dihydroquinoline (3C)*

The hydrate 3C, a metabolite of 7,8-dihydroquinoline (3A), was purified by preparative TLC (chloroform–methanol, 19:1), yield 16 mg (14 %);  $[\alpha]_{\text{D}} -18^\circ$  ( $c = 0.17$ ,  $\text{CHCl}_3$ ). The *e.e.* value (18 %) of the metabolite was determined by chiral stationary phase HPLC ( $\alpha$  1.12) (Chiralcel OB column, 25  $\times$  4.6 mm; 10 % propan-2-ol / hexane, 0.5 mL/min).

*5,6-Epoxy-5,6,7,8-tetrahydroquinoline (3D)*

Epoxide 3D was also separated from the unreacted substrate 3A by reversed phase TLC (methanol–water, 4:1), yield 11 mg (10 %). It was found to be an oil which did not appear to be optically active. Chiral stationary phase HPLC (conditions similar to those of its isomer) again resolved the epoxide 3D into its enantiomers ( $\alpha$  1.35) and confirmed the metabolite to be a racemic product.

*Chemical synthesis of reference compounds*

*5-Bromo-8-acetoxy-5,6,7,8-tetrahydroquinoline (3H).* A stirred solution of 8-acetoxyquinoline (3G)<sup>22</sup> (500 mg, 2.6 mmol) and  $\alpha,\alpha'$ -azoisobutyronitrile (5 mg) in carbon tetrachloride (25 mL), in the presence of N-bromosuccinimide (510 mg, 2.8 mmol) was irradiated for 30 min using a heat lamp. The reaction mixture was cooled, precipitated succinimide filtered off and the filtrate evaporated to yield the crude product as a mixture of isomers. Preparative TLC (methanol–chloroform, 1:25) gave a purified mixture of isomers (636 mg, 90 %), mp  $65^\circ$  (decomp.); (found: C 49.2; H 4.7; N 5.2.  $\text{C}_{11}\text{H}_{12}\text{O}_2\text{BrN}$

requires C, 48.9; H 4.4; N 5.2 %).  $\delta_{\text{H}}$  (250 MHz,  $\text{CDCl}_3$ ), 2.07(3H, s,  $\text{OCOCH}_3$ ), 2.24(2H, m, 7-H), 2.40(2H, m, 6-H), 5.53(1H, m, 5-H), 6.03(1H, t,  $J_{7,8}$  3.0 Hz, 8-H), 7.28(1H, dd,  $J_{3,4}$  8.1 Hz;  $J_{3,2}$  4.9 Hz, 3-H), 7.73(1H, dd,  $J_{4,2}$  1.8 Hz,  $J_{3,4}$  8.1 Hz, 4-H), 8.60(1H, dd,  $J_{2,4}$  1.8 Hz,  $J_{2,3}$  4.9 Hz, 2-H).

*8-Hydroxy-7,8-dihydroquinoline (3B).* The bromoacetate 3H (690 mg, 2.5 mmol) was stirred with sodium methoxide (1.5 g) in dry THF (25 mL) at  $0^\circ\text{C}$  for 1 h and then at room temperature for a further 2 h. Most of the THF was removed *in vacuo* and the residue treated with a saturated solution of sodium chloride (15 mL), extracted with chloroform, dried ( $\text{Na}_2\text{SO}_4$ ) and the solvent removed under reduced pressure. The crude hydrate 3B was purified by preparative TLC (ether), yield 200 mg, (33 %), mp  $49^\circ\text{C}$ ; (found:  $\text{M}^+$  147.0678  $\text{C}_9\text{H}_9\text{NO}$  requires 147.0684);  $\delta_{\text{H}}$  (250 MHz,  $\text{CDCl}_3$ ), 2.80(2H, m, 7-H), 4.20(1H, br; OH), 4.91(1H, dd,  $J_{8,6}$  3.9 Hz,  $J_{7,8}$  7.5 Hz, 8-H), 6.09(1H, m, 6-H), 6.45(1H, dd,  $J_{5,6}$  9.6 Hz,  $J_{5,7}$  3.2 Hz, 5-H), 7.17(1H, dd,  $J_{3,2}$  4.9 Hz,  $J_{3,4}$  7.5 Hz, 3-H), 7.36(1H, dd,  $J_{4,2}$  1.8 Hz,  $J_{4,3}$  7.5 Hz, 4-H), and 8.36(1H, d,  $J_{2,3}$  4.9 Hz, 2-H).

*5-Acetoxy-5,6,7,8-tetrahydroquinoline (2G).* A solution of alcohol 2F<sup>23</sup> (500 mg, 3.3 mmol), in acetic anhydride (1 mL) and pyridine (1 mL) containing *p*-dimethylaminopyridine (20 mg), was stirred at room temperature for 12 h. Pyridine and excess of acetic anhydride were removed by addition of toluene and subsequent distillation of the reaction mixture under reduced pressure. The acetate 2G was purified by flash chromatography to give a low melting solid (580 mg, 92 %) mp  $30\text{--}32^\circ\text{C}$  (hexane); (found: C 69.4; H 6.8; N 7 %.  $\text{C}_{11}\text{H}_{13}\text{O}_2\text{N}$  requires C 69.1; H 6.85; N 7.3 %);  $\delta_{\text{H}}$  (250 MHz,  $\text{CDCl}_3$ ), 2.03(4H, m, 6-H and 7-H), 2.09(3H, s,  $\text{OCOCH}_3$ ) 2.99(2H, m, 8-H), 6.00 (1H, t,  $J_{5,6}$  4.8 Hz, 5-H), 7.13(1H, dd,  $J_{2,3}$  4.8 Hz,  $J_{3,4}$  7.8 Hz, 3-H), 7.61(1H, dd,  $J_{4,2}$  1.4 Hz,  $J_{4,3}$  7.8 Hz, 4-H), and 8.48(1H, dd,  $J_{2,3}$  4.8 Hz,  $J_{2,4}$  1.4 Hz, 2-H).

*5-Acetoxy-8-bromo-5,6,7,8-tetrahydroquinoline (2H).* The acetate 2G (500 mg, 2.6 mmol) was converted to the bromoacetate 2H following the procedure described for the preparation of bromoacetate 3H. Preparative TLC (methanol–chloroform, 1:99) gave a purified mixture of isomers 2H, 550 mg (78 %), semi-solid; (found: C 48.6; H 4.5; N 5.1.  $\text{C}_{11}\text{H}_{12}\text{O}_2\text{BrN}$  requires C 48.9; H 4.4; N 5.2 %);  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ), 2.05(3H, s,  $\text{OCOCH}_3$ ), 2.30–2.80 (4H, m, 6-H and 7-H), 5.59(1H, m, 8-H), 6.08(1H, m, 5-H), 7.24 and 7.41(minor isomer) (1H, dd,  $J_{3,4}$  7.9 Hz,  $J_{2,3}$  4.7 Hz, 3-H), 7.70 and 8.31(minor isomer) (1H, dd,  $J_{4,2}$  1.6 Hz,  $J_{4,3}$  7.9 Hz, 4-H) and 8.62 and 8.78 (minor isomer) (1H, dd,  $J_{2,3}$  4.7 Hz,  $J_{2,4}$  1.6 Hz, 2-H).

*5-Hydroxy-5,6-dihydroquinoline (2B).* The bromoacetate 2H (800 mg, 3 mmol) was converted to the hydroxy compound 2B mp  $33\text{--}35^\circ\text{C}$  (ether), (250 mg, 55 %) using the same method as for the preparation of the hydroxydihydroquinoline 3B, (found:  $\text{M}^+$  147.0680,

C<sub>9</sub>H<sub>9</sub>NO requires 147.0684).  $\delta_{\text{H}}$ (250 MHz, CDCl<sub>3</sub>), 2.28(2H, m, 6-H), 4.32(1H, *brs*, OH), 4.46(1H, m, 5-H), 6.27(1H, m, 7-H), 6.63(1H, d,  $J_{7,8}$  9.8 Hz, 8-H), 7.20(1H, dd,  $J_{3,2}$  4.8 Hz,  $J_{3,4}$  6.2 Hz, 3-H), 7.73(1H, dd,  $J_{4,2}$  1.6 Hz,  $J_{4,3}$  6.2 Hz, 4-H), and 8.48(1H, dd,  $J_{2,3}$  4.8 Hz,  $J_{2,4}$  1.6 Hz, 2-H).

**6-Hydroxy-5,6,7,8-tetrahydroquinoline (2I).** A solution of 5,6-epoxy-5,6,7,8-tetrahydroquinoline **3D**<sup>19</sup> (400 mg, 2.72 mmol) in methanol (20 ml) was hydrogenated (12 h, room temperature, 1 atm) in the presence of 10 % Pd-C as catalyst (10 mg). After removal of the catalyst by filtration the methanol solution was concentrated *in vacuo*. The residue was crystallized from CH<sub>2</sub>Cl<sub>2</sub>-MeOH to yield the title compound **2I** (380 mg, 94 %), mp 134 °C; (found: C 72.0; H 7.7; N 9.1. C<sub>9</sub>H<sub>11</sub>NO requires C, 72.4; H 7.4; N 9.4 %),  $\delta_{\text{H}}$ (300 MHz, CDCl<sub>3</sub>), 1.93–2.16(2H, m, 7-H), 2.51(1H, *brs*, OH), 2.80(1H, dd,  $J_{5,5'}$  16.4 Hz,  $J_{5,6}$  7.3 Hz, 5-H), 2.94–3.16(3H, m, 5-H and 8-H), 4.20–4.26(1H, m, 6-H), 7.05(1H, dd,  $J_{3,4}$  7.7 Hz,  $J_{3,2}$  4.7 Hz, 3-H), 7.37(1H, d,  $J_{4,3}$  7.5 Hz, 4-H) and 8.36(1H, d,  $J_{2,3}$  4.7 Hz, 2-H).

**6-tert-Butyldimethylsilyloxy-5,6,7,8-tetrahydroquinoline (2J).** *tert*-Butyldimethylsilyltrifluoromethane sulphonate (580 mg, 2.2 mmol) was added to a solution of 6-hydroxy-5,6,7,8-tetrahydroquinoline (**2I**) (300 mg, 2.0 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> solvent (20 ml) containing triethylamine (0.5 mL) at 0 °C under nitrogen. The reaction mixture was stirred at 0 °C for 0.5 h and then at room temperature overnight. The solvent was removed under reduced pressure and the residue treated with a saturated solution of aqueous sodium bicarbonate (10 mL). The reaction mixture was extracted with diethyl ether (3 × 25 mL), the combined extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to yield the crude product **2J**. Purification of the crude product by flash chromatography afforded the pure compound **2J** (0.473 g, 90 %) bp 112 °C at 1.5 mm Hg; (found: C 68.7; H 9.7; N 4.7 C<sub>15</sub>H<sub>25</sub>NOSi requires C 68.4; H 9.6; N 5.3 %);  $\delta_{\text{H}}$  (300 MHz, CDCl<sub>3</sub>) 0.08(3H, s, SiCH<sub>3</sub>), 0.10(3H, s, SiCH<sub>3</sub>), 0.88(9H, s, SiC(CH<sub>3</sub>)<sub>3</sub>), 1.90–2.02(2H, m, 7-H), 2.75(1H, dd,  $J_{5,5'}$  16.5 Hz,  $J_{5,6}$  7.3 Hz, 5-H), 2.88–2.97(3H, m, 5'-H and 8-H), 3.06–3.14(1H, m, 8'-H), 4.12–4.17(1H, m, 6-H), 7.02(1H, dd,  $J_{3,4}$  7.6 Hz,  $J_{3,2}$  4.8 Hz, 3-H), 7.33(1H, d,  $J_{4,3}$  7.6 Hz, 4-H) and 8.35(1H, d,  $J_{2,3}$  4.8 Hz, 2-H).

**8-Bromo-6-tert-butyldimethylsilyloxy-5,6,7,8-tetrahydroquinoline (2K).** A freshly distilled sample of 6-*tert*-butyldimethylsilyloxy-5,6,7,8-tetrahydroquinoline (**2J**) (450 mg, 1.71 mmol) was brominated with *N*-bromosuccinimide (310 mg, 1.74 mmol) using the procedure described in the preceding experimental section. The silyloxy derivative **2K** was obtained as a light yellow oil (520 mg, 89 %) and was used without further purification in the next stage due to its unstable nature; (found: [M-CH<sub>3</sub>]<sup>+</sup> 326.05822. C<sub>14</sub>H<sub>21</sub><sup>79</sup>BrNOSi requires 326.05762).  $\delta_{\text{H}}$  (300 MHz, CDCl<sub>3</sub>) (major isomer) 0.09 (6H, s, Si(CH<sub>3</sub>)<sub>2</sub>), 0.84 (9H, s, SiC(CH<sub>3</sub>)<sub>3</sub>), 1.86–1.93 (1H, m, 7-H), 2.37–2.48 (1H, m, 7-H), 2.84–2.93 (1H, m, 5-H), 3.08–3.14 (1H, m, 5-H), 4.31–4.34 (1H, m, 6-

H), 4.93–4.94 (1H, m, 8-H), 7.05 (1H, dd,  $J_{3,4}$  7.7 Hz,  $J_{3,2}$  4.8 Hz, 3-H), 7.56 (1H, d,  $J_{4,3}$  7.7 Hz, 4-H) and 8.36 (1H, dd,  $J_{2,3}$  4.8 Hz,  $J_{2,4}$  1.5 Hz, 2-H).

**6-tert-Butyldimethylsilyloxy-5,6-dihydroquinoline (2L).** To a stirred solution of the silyloxy derivative **2K** (520 mg, 1.52 mmol) in dry THF (20 mL) was added an excess of DBN (1.6 mL, 2 mmol) at 0 °C under nitrogen. After stirring the reaction mixture for 4 h at 0 °C water (10 mL) was added and THF was removed under reduced pressure. The resulting reaction mixture was thoroughly extracted with ethyl acetate (3 × 25 mL), the organic extract dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. The crude product was purified by preparative TLC (hexane-diethyl ether, 7:3) to give the product **2L** (278 mg, 70 %) as a viscous oil, bp 102 °C at 1.2 mm Hg; (found M<sup>+</sup> 261.15379. C<sub>15</sub>H<sub>23</sub>NOSi requires 261.15488).  $\delta_{\text{H}}$ (300 MHz, CDCl<sub>3</sub>), 0.07(3H, s, Si(CH<sub>3</sub>)), 0.09(3H, s, Si(CH<sub>3</sub>)), 0.89(9H, s, -SiC(CH<sub>3</sub>)<sub>3</sub>), 2.92–3.01(2H, m, 5-H), 4.68–4.69(1H, m, 6-H), 6.22(1H, dd,  $J_{7,8}$  9.8 Hz,  $J_{7,6}$  3.0 Hz, 7-H), 6.60(1H, dd,  $J_{8,7}$  9.8 Hz,  $J_{8,6}$  0.8 Hz, 8-H), 7.03(1H, dd,  $J_{3,4}$  7.6 Hz,  $J_{3,2}$  5.0 Hz, 3-H), 7.41(1H, dd,  $J_{4,3}$  7.7 Hz,  $J_{4,2}$  1.4 Hz, 4-H) and 8.37(1H, dd,  $J_{2,3}$  5.0 Hz,  $J_{2,4}$  1.3 Hz, 2-H).

**6-Hydroxy-5,6-dihydroquinoline (2C).** A solution of the TBDMS ether **2L** (200 mg, 0.76 mmol) in anhydrous THF (10 mL) was treated with tetrabutylammonium fluoride (2 mL, 1 M solution in THF) at 0 °C under nitrogen and the reaction mixture stirred at room temperature for 24 h. After removal of the solvent a saturated solution of sodium chloride (10 mL) was added to the residue and the aqueous reaction mixture extracted with ethyl acetate (3 × 25 mL). The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent removed under reduced pressure to give the crude arene hydrate **2C**. Purification by preparative TLC (chloroform-methanol, 24:1) gave the 6-hydroxy-5,6-dihydroquinoline (**2C**) as a colourless oil (63 mg, 56 %). (found: M<sup>+</sup> 147.0687. C<sub>9</sub>H<sub>9</sub>NO requires 147.0684);  $\delta_{\text{H}}$ (300 MHz, CDCl<sub>3</sub>), 3.08(2H, d,  $J_{5,6}$  6.0 Hz, 5-H), 4.53–4.54(1H, m, 6-H), 6.40(1H, dd,  $J_{7,8}$  9.8 Hz,  $J_{7,6}$  4.4 Hz, 7-H), 6.73(1H, d,  $J_{8,7}$  9.8 Hz, 8-H), 7.08(1H, dd,  $J_{3,4}$  7.4 Hz,  $J_{3,2}$  4.9 Hz, 3-H), 7.46(1H, d,  $J_{4,3}$  7.5 Hz, 4-H) and 8.41(1H, d,  $J_{2,3}$  4.8 Hz, 2-H). On chiral stationary phase HPLC, using a Chiracel OB column (25 cm × 4.6 mm, 10 % propan-2-ol/hexane, 0.5 mL min<sup>-1</sup>), hydrate **2C** showed a partial separation of the enantiomers ( $\alpha$  1.24).

**7-Hydroxy-5,6,7,8-tetrahydroquinoline (3I).** The title compound **3I** was obtained in 97 % yield (688 mg) by catalytic hydrogenation (10 % Pd-C) of 7,8-epoxy-5,6,7,8-tetrahydroquinoline (**2D**)<sup>19</sup> (700 mg, 4.76 mmol), mp 76–77 °C, (found: C 72.2; H 7.6; N 9.2. C<sub>9</sub>H<sub>11</sub>NO requires C 72.5; H 7.4; N 9.4 %);  $\delta_{\text{H}}$ (300 MHz, CDCl<sub>3</sub>), 1.85–2.06(2H, m, 6-H), 2.75–2.83(1H, m, 5-H), 2.90(2H, m, 5'-H and 8-H), 3.24(1H, dd,  $J_{8,8'}$  17.2 Hz,  $J_{8,7}$  4.8 Hz, 8'-H), 4.25–4.29(1H, m, 7-H), 7.04(1H, dd,  $J_{3,4}$  7.6 Hz,  $J_{3,2}$  4.8 Hz, 3-H), 7.39(1H, d,  $J_{4,3}$  7.6 Hz, 4-H), and 8.34(1H, d,  $J_{2,3}$  4.8 Hz, 2-H).

**7-tert-Butyldimethylsilyloxy-5,6,7,8-tetrahydroquinoline (3J).** The silyl ether **3J** was prepared, in 92 % yield (763 mg), colourless oil, bp 110 °C at 1.2 mm Hg, from the hydroxy compound **3I** following the method described for the synthesis of isomeric silyl ether **2J**. (found: C 68.6; H 9.8; N 5.4.  $C_{15}H_{25}NOSi$  requires C 68.4; H 9.6; N 5.3 %);  $\delta_H$  (300 MHz,  $CDCl_3$ ) 0.07(3H, s,  $-SiCH_3$ ), 0.073(3H, s,  $-SiCH_3$ ), 0.10(9H, s,  $-SiC(CH_3)_3$ ), 1.80–1.97(2H, m, 6-H), 2.70–2.77(1H, m, 5-H), 2.86–2.99(2H, m, 5'-H and 8-H), 3.14(1H, dd,  $J_{8,8}$  17.4 Hz,  $J_{8,7}$  4.6 Hz, 8'-H), 4.21–4.25(1H, m, 7-H), 7.03(1H, dd,  $J_{3,4}$  7.5 Hz,  $J_{3,2}$  4.8 Hz, 3-H), 7.36(1H, d,  $J_{4,3}$  7.6 Hz, 4-H) and 8.36(1H, d,  $J_{2,3}$  4.8 Hz, 2-H).

**5-Bromo-7-tert-butyldimethylsilyloxy-5,6,7,8-tetrahydroquinoline (3K).** The silyl ether **3J** (526 mg, 2 mmol) was brominated, in an identical manner to that described for isomeric silyl ether **2J**, to yield the bromo silyl ether **3K** (613 mg, 90 %) as a light yellow oil. Preparative TLC of the crude product (hexane–diethyl ether, 7:3) separated the diastereoisomers. The major isomer **3K** (80 %) was isolated as a white solid, mp 76 °C (diethyl ether–hexane); (found:  $[M-CH_3]^+$  326.05888.  $C_{14}H_{21}^{79}BrNOSi$  requires 326.05762).  $\delta_H$  (300 MHz,  $CDCl_3$ ) 0.14 (6H, s,  $Si(CH_3)_2$ ), 0.91 (9H, s,  $SiC(CH_3)_3$ ) 2.21–2.31(1H, m, 6-H), 2.45–2.52(1H, m, 6'-H), 2.96(1H, dd,  $J_{8,8}$  17.3 Hz,  $J_{8,7}$  8.9 Hz, 8-H), 3.37(1H, dd,  $J_{8,8}$  17.2 Hz,  $J_{8,7}$  5.9 Hz, 8'-H), 4.57–4.63(1H, m, 7-H), 5.53(1H, dd,  $J_{5,6}$  =  $J_{5,6'}$  4.2 Hz, 5-H), 7.14(1H, dd,  $J_{3,4}$  7.8 Hz,  $J_{3,2}$  4.7 Hz, 3-H), 7.69(1H, dd,  $J_{4,3}$  7.8 Hz,  $J_{4,2}$  1.3 Hz, 4-H) and 8.46(1H, dd,  $J_{2,3}$  4.7 Hz,  $J_{2,4}$  1.4 Hz, 2-H). Minor isomer **3K**, an oil,  $\delta_H$  (300 MHz,  $CDCl_3$ ) 0.11 (6H, s,  $Si(CH_3)_2$ ), 0.92 (9H, s,  $SiC(CH_3)_3$ ) 2.33–2.44(1H, m, 6-H), 2.67–2.75(1H, m, 6'-H), 3.01(1H, dd,  $J_{8,8}$  16.8 Hz,  $J_{8,7}$  9.5 Hz, 8-H), 3.17(1H, dd,  $J_{8,8}$  16.8 Hz,  $J_{8,7}$  6.9 Hz, 8'-H), 3.99–4.06(1H, m, 7-H), 5.30–5.39(1H, m, 5-H), 7.16(1H, dd,  $J_{3,4}$  8.0 Hz,  $J_{3,2}$  4.8 Hz, 3-H), 7.91(1H, d,  $J_{4,3}$  7.9 Hz, 4-H) and 8.43(1H, dd,  $J_{2,3}$  4.4 Hz,  $J_{2,4}$  0.80 Hz, 2-H).

**7-tert-Butyldimethylsilyloxy-7,8-dihydroquinoline (3L).** Following the same experimental procedure as used for the preparation of the isomeric silyl ether derivative **2L**, the title compound **3L** was prepared from the crude bromosilyl ether mixture **3K** (600 mg, 1.76 mmol) in 74 % yield (340 mg), a viscous oil, (found:  $M^+$  261.15387.  $C_{15}H_{23}NOSi$  requires 261.15488).  $\delta_H$  (300 MHz,  $CDCl_3$ ) 0.11(3H, s,  $-SiCH_3$ ), 0.15(3H, s,  $-SiCH_3$ ), 0.89(9H, s,  $-SiC(CH_3)_3$ ), 2.41(1H, dd,  $J_{8,8}$  17.3 Hz,  $J_{8,7}$  7.8 Hz, 8-H), 2.67(1H, dd,  $J_{8,8}$  17.2 Hz,  $J_{8,7}$  3.4 Hz, 8'-H), 4.75–4.76(1H, m, 7-H), 6.02(1H, dd,  $J_{6,5}$  9.7 Hz,  $J_{6,7}$  3.3 Hz, 6-H), 6.39(1H, dd,  $J_{5,6}$  9.7 Hz,  $J_{5,7}$  1.3 Hz, 5-H), 7.09(1H, dd,  $J_{3,4}$  7.3 Hz,  $J_{3,2}$  4.8 Hz, 3-H), 7.29(1H, d,  $J_{3,4}$  7.3 Hz, 4-H) and 8.31(1H, d,  $J_{2,3}$  4.7 Hz, 2-H).

**7-Hydroxy-7,8-dihydroquinoline (3C).** The hydrate **3C** was obtained from the TBDMS ether precursor **3L** (200 mg, 0.77 mmol) in 61 % yield (69 mg) as an oil, following the method described for the preparation of isomeric hydrate **2C**; (found:  $M^+$ , 147.0687,  $C_9H_9NO$  requires 147.0684).  $\delta_H$  (300 MHz,  $CDCl_3$ ), 3.18(2H, dd,  $J_{8,8}$  14.1 Hz,  $J_{8,7}$  7.0

Hz, 8-H), 4.55–4.59(1H, m, 7-H), 6.14(1H, dd,  $J_{6,5}$  9.5 Hz,  $J_{6,7}$  4.5 Hz, 6-H), 6.47(1H, d,  $J_{5,6}$  9.5 Hz, 5-H), 7.05(1H, dd,  $J_{3,4}$  7.5 Hz,  $J_{3,2}$  4.9 Hz, 3-H), 7.30(1H, d,  $J_{4,3}$  7.5 Hz, 4-H) and 8.28(1H, d,  $J_{2,3}$  4.8 Hz, 2-H). Arene hydrate **3C** also showed partial separation of the enantiomers ( $\alpha$  1.12) when analysed by chiral stationary phase HPLC under conditions identical to those used for the analysis of hydrate **2C**.

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