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The preparation and some chemistry of 2,2-dimethyl-1,2-dihydroquinolines

Natalie M. Williamson and A. David Ward*

Department of Chemistry, University of Adelaide, Adelaide, SA 5005, Australia

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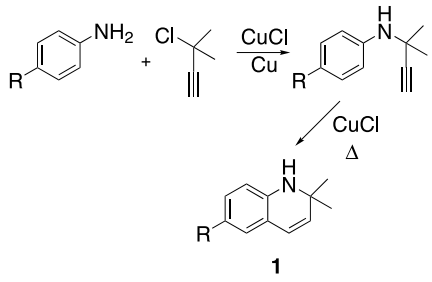
Abstract—The cyclisation of *N*-(1,1-dimethylpropargyl) anilines, using cuprous chloride in refluxing toluene, yields 6-substituted-2,2-dimethyl-1,2-dihydroquinolines. The reactivity of the double bond in the heterocyclic ring of these products is exemplified by chlorination, to yield 6-substituted-3,4-*cis*-dichloro-2,2-dimethyl-1,2,3,4-tetrahydroquinolines which can be selectively dechlorinated to provide 6-substituted-3-chloro-2,2-dimethyl-1,2,3,4-tetrahydroquinolines; epoxidation to yield an epoxide, which can be hydrogenolysed to the corresponding 3-hydroxy product and in turn oxidised to the 3-keto derivative; and oxymercuration to provide a 4-hydroxy product and hence a 4-keto derivative. Dehydrochlorination of a 3,4-dichloro product provides a 3-chloro-1,2-dihydroquinoline which can be hydrolysed to a 3-keto system. The formation of *cis* 3,4-dichloro products from the chlorination, as well as the formation of a *cis* chlorohydrin from the chlorination of *N*-acetyl-2,2,6-trimethyl-1,2-dihydroquinoline in partially aqueous solution, suggests that *N*-acetyl, or *N*-trifluoroacetyl groups, participate in the addition process.

1. Introduction

The availability of 2,2-disubstituted-1,2-dihydroquinolines,[1–3] **1**, via the copper catalysed cyclisation of *N*-(1,1-substitutedpropargyl) anilines,[4,5] (Scheme 1) makes these compounds of interest as starting materials for the preparation of 2,2,3,4- and 2,2,3- or 2,2,4-substituted tetrahydroquinolines and related compounds. We have been interested for some time[3,6–9] in the development of general synthetic approaches to analogues of the antiviral compound Virantmycin,[10–16] **2**, and we were, as a consequence, particularly interested in methodology that would lead to 2,2-disubstituted-3-chlorotetrahydroquinolines. We have previously noted[5] that the size of the substituents attached to the carbon bearing the nitrogen atom affects the coupling of the amine to the acetylenic chloride (Scheme 1) such that when these groups are sufficiently bulky the coupling does not occur and for this reason we chose initially to investigate the chemistry of 2,2-dimethyl-1,2-dihydroquinolines in order to establish the range of reactions that these least sterically hindered 2,2-substituted-1,2-dihydroquinolines would undergo. Any addition reaction to the double bond that creates a 3-substituted product has also created a neopentyl system at the 3-position which has ramifications for substitutions at this position. Having established the chemistry of the dimethyl substituted dihydroquinolines we would then be in a position to evaluate how well these reactions would work when more bulky substituents, needed for the development of Virantmycin analogues, were present.



Scheme 1.

2. Results and discussion

Chlorination of the dihydroquinolines, **1**, was expected to be difficult to control as, at least in cases where an aromatic substituent that is electron donating is present, chlorination of both the double bond and the aromatic ring would be expected. Even the *N*-acetyl compound, **3**, gave the expected dichloro compound, **4**, together with some of the ring chlorinated material, **5**. Aromatic chlorination did not occur, however, when the N-protecting group was trifluoroacetyl rather than acetyl. Consequently a range of

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* Corresponding author. Tel.: +61 8 8303 5496; fax: +61 8 8303 4358; e-mail: david.ward@adelaide.edu.au

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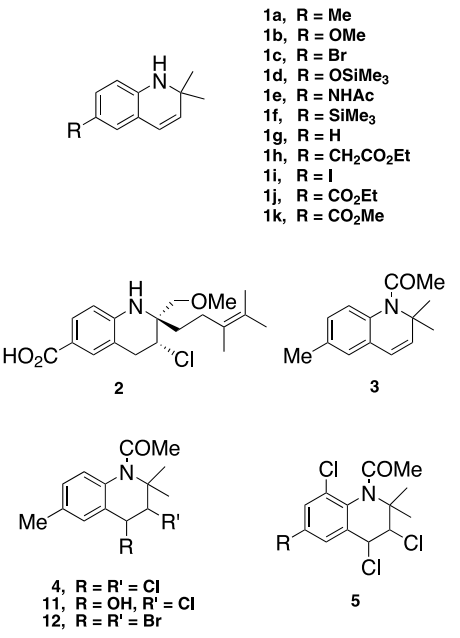
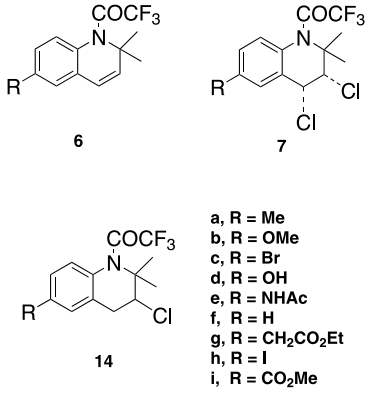
N-trifluoroacetyl derivatives, **6a**–**6h**, were prepared to investigate the reactivity of the dichloro compounds.

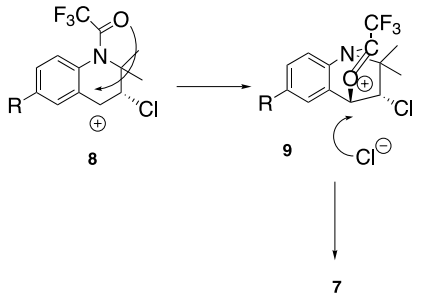


The ester-substituted dihydroquinoline, **1j**, cannot be N-protected due to the delocalisation of the lone electron pair on the nitrogen atom by the ester substituent. Attempts to chlorinate the dihydroquinoline double bond of the unprotected ester, **1j**, resulted in a complex mixture. However the iodo-substituted dihydroquinoline, **6h**, could be carbonylated to yield the methyl ester, **6i**, in moderate yield as well as a small amount of the deprotected compound, **1k**. This deprotection possibly involves methanolysis of the trifluoroacetamide facilitated by the triethylamine present in the reaction mixture.



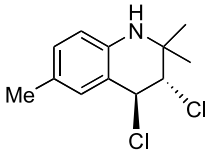
Chlorination of the *N*-trifluoroacetyldihydroquinolines **6a**–**6i** proceeded smoothly to give excellent yields of the 3,4-dichlorotetrahydroquinolines, **7a**–**7i**. The ^{1}H NMR spectra of the dichloro compounds showed two doublets at approximately δ 4.5 and 5.2, corresponding to the two methine hydrogens attached to chlorine-bearing carbon atoms. The coupling constants for these doublets were small, ranging from 4–6 Hz, suggesting *cis* stereochemistry. By the same criteria *cis* chlorination was also observed for the *N*-acetyl compound, **3**, and for its corresponding 6-methoxy substituted analogue.

This *cis* geometry of these dichlorotetrahydroquinolines, **7**, can be rationalised by invoking the participation of the N-protecting group, as shown in Scheme 2. The benzylic carbocation, **8**, and/or the corresponding chloronium ion, may be trapped by the carbonyl oxygen of the acyl group, giving the *trans*-intermediate, **9**, which is then attacked at the benzylic position by chloride ion to give the *cis*-product.



Scheme 2.

Support for this protecting-group participation explanation was provided by the chlorination, in acidic solution, of the unprotected dihydroquinoline, **1a**, which gave a dichloro product, **10**, whose coupling constant, $J_{3,4}$, was 9.2 Hz, typical of that expected for a *trans* product and showing that in the absence of the protecting group the chlorination proceeds via the expected chloronium ion mechanism.

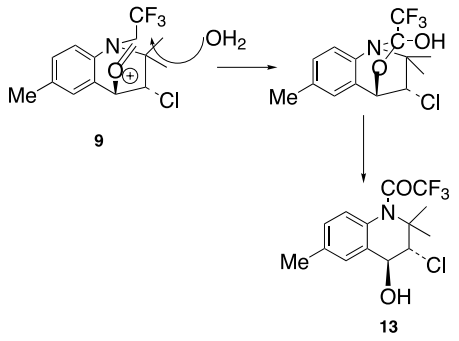


The dichloro compounds, **7**, were, in general, unstable and were used as soon as they had been isolated. The *N*-acetyldichloro compound, **4**, slowly crystallised on standing exposed to the atmosphere. Recrystallisation of this material gave the alcohol, **11**, whose structure, and the *trans* geometry of the chlorine and hydroxyl groups in the heterocyclic ring, were confirmed by an X-ray crystal structure determination.[17] In the solid state the heterocyclic ring is in a twist boat conformation. Such a conformation in solution would facilitate substitution of the benzylic chlorine by the carbonyl oxygen of either the acetyl or the trifluoroacetyl group. The coupling constant, $J_{3,4}$, was 9.7 Hz for the *trans* chlorohydrin, **11**, a value which is very similar to that of the *trans* dichloride, **10**, but considerably higher than the coupling constants of the *cis* dichlorides, **7**.

Bromination of the *N*-acetyl dihydroquinoline, **3**, gave an unstable dibromo compound, **12**, in high yield. A coupling constant of 3.9 Hz for the H3 and H4 doublets suggested that *cis*-addition had also occurred with bromine.

The facile conversion of the dichloride, **4**, to the chlorohydrin, **11**, prompted an examination of the chlorination in partially aqueous solvents. When the chlorination

of **3** was conducted in a tetrahydrofuran/water mixture the chlorohydrin, **11**, was produced in 96% yield. The *N*-trifluoroacetyl compound, **6a**, gave only a 36% yield of the corresponding chlorohydrin, **13**, under these conditions but the *cis*-3,4-dichloro compound, **7a**, was also obtained in a 47% yield. The *trans* geometry of the chlorohydrins, **11** and **13**, can either arise from the displacement of the benzylic chlorine in the *cis* dichloride or from attack on the intermediate, **9**, as shown in Scheme 3.

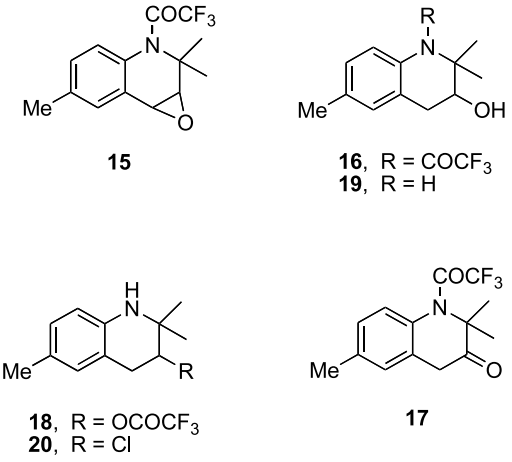


Scheme 3.

Treatment of the dichloro compounds, **7**, with zinc-modified cyanoborohydride[18] gave the corresponding 3-chlorotetrahydroquinolines, **14**, in moderate to excellent yields. The nature of the aromatic substituent was found to affect the rate of dechlorination, with electron-withdrawing substituents such as bromo, iodo and ester groups slowing the reaction to such an extent that only 50% conversion was observed after 10–12 days reaction time. Two doublet of doublets in the region δ 3.0–3.2, both with a large geminal coupling constant (15–16 Hz) and a smaller vicinal coupling constant (3–6 Hz), and a third doublet of doublets, at approximately δ 4.2, with two small vicinal coupling constants confirmed the removal of the benzylic chlorine in these products.

Epoxidation of the double bond of **6a**, to yield the epoxide **15**, was achieved using *meta*-chloroperoxybenzoic acid. Hydrogenolysis of the epoxide provided the alcohol, **16**, in good yield. The ^{1}H NMR spectrum of **16** resembled that of the related 3-chloro system, **14a**.

Oxidation of the alcohol, **16**, to the ketone, **17**, proceeded smoothly using Jones reagent. However, the ^{1}H NMR spectrum of the ketone did not show the expected sharp signals for the geminal dimethyl groups or the hydrogens of the benzylic methylene group, but rather four very broad singlets at δ 1.3, 1.7, 3.3 and 3.8, respectively, suggesting that a ring flipping process of the heterocyclic ring was creating two separate magnetic environments for the hydrogens attached to it, causing the broadening observed at room temperature. Heating the NMR sample to 50 °C saw coalescence of the two pairs of broadened signals to single resonances at δ 1.51 and 3.58, assigned to the hydrogens of the geminal dimethyl groups and the benzylic methylene group respectively. Cooling the sample to 0 °C caused all signals to sharpen considerably with the signals for the hydrogens of the two geminal dimethyl groups now appearing as two sharp singlets at δ 1.34 and 1.70, while the diastereotopic hydrogens of the benzylic methylene group were now well-defined doublets at δ 3.36 and 3.87. The signal for H5 was at δ 7.11.

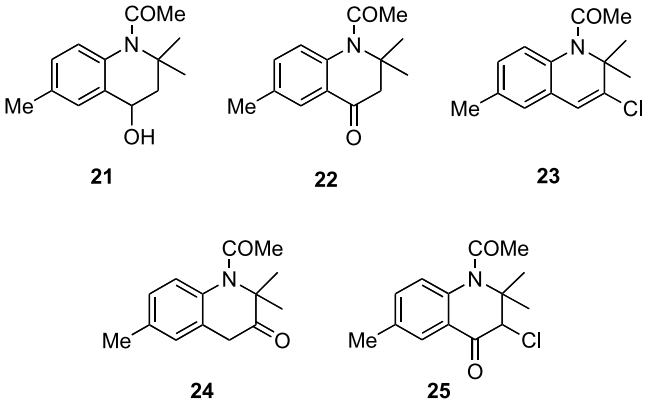


The alcohol, **16**, was subjected to Mitsunobu conditions in attempts to introduce a halogen atom into the 3-position. However using zinc chloride and tetrabutylammonium bromide or chloride as the halide source produced only the trifluoroacetate, **18**, presumably formed via trifluoroacetyl group transfer from the nitrogen atom to the oxygen atom. TLC and ^{1}H NMR of a sample of the alcohol, **16**, that had been standing for a few weeks revealed that the trifluoroacetyl transfer from the nitrogen atom to the oxygen atom is a relatively facile process as it also occurs on standing. Hydrolysis of the trifluoroacetate, **18**, using 10% methanolic potassium bicarbonate, provided the aminoalcohol, **19**. Treatment of this aminoalcohol with thionyl chloride[13] gave only an intractable product mixture as evidenced by tlc and ^{1}H NMR in which signals for the expected chloro compound could not be detected.

Direct S_N2 displacement of the trifluoroacetyl moiety of **18** with chloride ion (using tetrabutylammonium chloride as the chloride source) was very slow and the 3-chloroquinoline product, **20**, was unable to be separated from the starting trifluoroacetate. Evidence for the presence of the chloro compound, **20**, was seen in the ^{1}H NMR of the crude mixture. Two doublet of doublets were observed at δ 5.10 and 4.08, assigned to the methine hydrogen atoms of the trifluoroacetate, **18**, and the monochloride, **20**, respectively. A mass spectrum of the mixture showed molecular ions for both the trifluoroacetate, **18**, (*m*/*z* 287) and the chloro compound, **20**, (*m*/*z* 209/211).

It was also of interest to establish whether the double bond in the heterocyclic ring of the dihydroquinoline systems could undergo hydration and, if so, which carbon of the double bond was functionalised. Hydroboration of **3** gave a mixture of the *N*-ethyldihydroquinoline from reduction of the amide together with starting material. Hydroboration of the unprotected amine, **1a**, with excess diborane was unsuccesful with starting material being recovered. Oxymercuration of **3** gave a poor yield of an alcohol, **21**, whose NMR spectrum was quite different to that of the alcohol, **16**. In particular, the benzylic methylene hydrogens of **16** occur as two doublet of doublets at δ 2.82 and 2.94, with both

showing a vicinal and a geminal coupling, whereas the methylene signals of **21** were less deshielded and appeared as a multiplet in the region δ 2.1–2.4. The structure of this alcohol was confirmed by its oxidation to the ketone, **22**, in which the NMR signal for H5 showed the characteristic downfield shift (δ 7.75) expected for the anisotropic effect of the adjacent carbonyl. Oxidation of the chlorohydrin, **11**, gave the corresponding ketone, **25**, whose H5 signal in the NMR spectrum was at δ 7.85 (d, $J=2$ Hz).



The dichloride, **4**, could be dehydrochlorinated using potassium tertiary butoxide and gave the vinyl chloride, **23**. Confirmation of this structure was provided by its hydrolysis to the ketone, **24**, in which the NMR signal for H5 was at ca δ 7.2.

3. Conclusion

6-Substituted 2,2-dimethyl-1,2-dihydroquinolines can be readily prepared by the cyclisation of 4-substituted *N*-(1,1-dimethylpropargyl)anilines using cuprous chloride in refluxing toluene. These dihydroquinolines serve as convenient substrates from which to prepare 3-, 4- and 3,4-functionalised 2,2-dimethyl-1,2,3,4-tetrahydroquinolines with substituents at the 6-position of the quinoline system.

4. Experimental

4.1. General

Melting points were determined on a Kofler hot stage apparatus equipped with a Reichert microscope and are uncorrected. Infrared spectra were recorded on a Jasco A102 grating spectrometer. *N*-acetyl-tetrahydro- and dihydroquinolines and *N*-trifluoroacetyl-tetrahydro- and dihydroquinolines showed carbonyl absorption in the region 1680–1705 cm^{-1}. The double bond in the heterocyclic ring of the dihydroquinolines absorbed in the region 1630–1640 cm^{-1}. The NH of N-unsubstituted di- and tetrahydroquinolines absorbed in the region 3370–3400 cm^{-1}. Only absorptions above 1600 cm^{-1}, other than those, are provided for individual compounds. Proton NMR spectra (δ_H) were recorded on a Bruker ACP300 spectrometer operating at 300 MHz in deuterochloroform solution using tetramethylsilane as an internal standard. Chemical shifts are quoted as δ in parts per million and coupling constants (J) are given in Hertz (Hz). Electron impact mass spectra (m/z) were recorded at 70 eV on a VG ZAB 2HF spectrometer. Accurate mass measurements (HRMS) were made using electron impact on either an AEI MS3074 spectrometer or by the University of Melbourne on a JEOL AX505H spectrometer. Where a formula contains bromine or chlorine atoms the accurate mass measurement was conducted on the major molecular ion peak corresponding to the halogen atom (or atoms) of lowest atomic weight. Flash chromatography refers to nitrogen pressure driven rapid chromatography[19] using Merck silica gel, pore diameter 60A. Organic extracts were dried using anhydrous magnesium sulfate.

4.2. General procedure for the synthesis of 2,2-dimethyl-1,2-dihydroquinolines 1a–1j

A stirred mixture of the N-substituted aniline[4,5] (11 mmol) and cuprous chloride (250 mg) in toluene (10 mL) was refluxed under an atmosphere of nitrogen for 0.5–16 h. The reaction mixture was cooled and water (10 mL) was added. The organic phase was separated and combined with the dichloromethane extracts of the aqueous phase. The combined organic extracts were dried and the solvent removed. The residue was purified by flash chromotography; elution with light petroleum/ethyl acetate gave the dihydroquinolines, which partially decomposed, and/or rearranged, on attempted distillation under reduced pressure. By this method the following compounds were prepared:

4.2.1. 2,2,6-Trimethyl-1,2-dihydroquinoline 1a. (56%) as white needles, mp 36–37 °C (lit.[3] mp 36–37 °C).

4.2.2. 6-Methoxy-2,2-dimethyl-1,2-dihydroquinoline 1b. (41%) as a yellow oil; δ_H 6.35–6.60 (3H, m, ArH), 6.20 (1H, d, $J=9.1$ Hz, C=CH), 5.45 (1H, d, $J=9.1$ Hz, C=CH), 3.70 (3H, s, OMe), 2.25 (1H, br s (exchanges with D_2O), NH), 1.25 (6H, s, Me); m/z 189 (M, 20%), 174 (100), 159 (15), 131 (40); HRMS: M, found 189.1150. $C_{12}H_{15}NO$ requires 189.1154.

4.2.3. 6-Bromo-2,2-dimethyl-1,2-dihydroquinoline 1c. (43%) as orange prisms, mp 59–61 °C; δ_H 6.9–7.1 (2H, m, ArH), 6.28 (1H, d, $J=8.3$ Hz, ArH), 6.18 (1H, d, $J=9.7$ Hz, C=CH), 5.49 (1H, d, $J=9.7$ Hz, C=CH), 3.50 (1H, br s (exchanges with D_2O), NH), 1.29 (6H, s, Me); m/z 237/239 (M, 15%), 222/224 (100), 143 (50); HRMS: M, found 237.0146. $C_{11}H_{12}BrN$ requires 237.0153.

4.2.4. 2,2-Dimethyl-6-trimethylsilyloxy-1,2-dihydroquinoline 1d. (54%) as an unstable orange oil; δ_H 6.49 (1H, dd, $J=2.7$, 8.3 Hz, ArH), 6.43 (1H, d, $J=2.7$ Hz, ArH), 6.31 (1H, d, $J=8.3$ Hz, ArH), 6.20 (1H, d, $J=9.6$ Hz, C=CH), 5.50 (1H, d, $J=9.6$ Hz, C=CH), 3.50 (1H, br s (exchanges with D_2O), NH), 1.28 (6H, s, Me), 0.22 (9H, s, $SiMe_3$); m/z 247 (M, 15%), 232 (100), 160 (25), 73 (10); HRMS: M, found 247.1385. $C_{14}H_{21}NOSi$ requires 247.1392.

4.2.5. *N*-(2,2-Dimethyl-1,2-dihydro-6-quinolyl)acetamide 1e. (78%) as an orange oil. ν_{max} ($CDCl_3$) 1675 cm^{-1};

δ_H 7.98 (1H, br s (exchanges with D_2O), NH amide), 6.87–7.05 (2H, m, ArH), 6.33, (1H, d, J=8.2 Hz, ArH), 6.15 (1H, d, J=9.8 Hz, C=CH), 5.48 (1H, d, J=9.8 Hz, C=CH), 3.50 (1H, br s (exchanges with D_2O), NH amine), 2.02 (3H, s, COMe), 1.24 (6H, s, Me); *m/z* 216 (M, 15%); 201 (100); 160 (10); 159 (15); HRMS: M, found 216.1252. $C_{13}H_{16}N_2O$ requires 216.1263.)

4.2.6. 2,2-Dimethyl-6-trimethylsilyl-1,2-dihydroquinoline 1f. (30%) as an unstable orange oil; δ_H 7.07 (2H, m, ArH), 6.39 (1H, d, J=9.7 Hz, C=CH), 6.26 (1H, d, J=9.5 Hz, ArH), 5.45 (1H, d, J=9.7 Hz, C=CH), 3.70 (1H, br s (exchanges with D_2O), NH), 1.30 (6H, s, Me), 0.20 (9H, s, $SiMe_3$); *m/z* 231 (M, 1%), 216 (2), 178 (3), 158 (20), 144 (100).

4.2.7. 2,2-Dimethyl-1,2-dihydroquinoline 1g. Obtained from the same reaction. (21%) as an orange oil; δ_H 6.95 (1H, t, J=7.9 Hz, ArH), 6.87 (1H, d, J=7.5 Hz, ArH), 6.57 (1H, t, J=7.5 Hz, ArH), 6.40 (1H, d, J=7.9 Hz, ArH), 6.26 (1H, d, J=9.6 Hz, C=CH), 5.46 (1H, d, J=9.6 Hz, C=CH), 3.64 (1H, br s (exchanges with D_2O), NH), 1.30 (6H, s, Me); *m/z* 159 (M, 15%), 145 (15), 144 (100), 143 (10), 128 (5); HRMS: M, found 159.1043. $C_{11}H_{13}N$ requires 159.1048.

4.2.8. Ethyl 2-(2,2-dimethyl-1,2-dihydro-6-quinolyl)acetate 1h. (57%) as an unstable orange oil; ν_{max} ($CDCl_3$) 1720 cm^{-1}; δ_H 6.87 (1H, dd, J=1.9, 8.0 Hz, ArH), 6.80 (1H, d, J=1.9 Hz, ArH), 6.36 (1H, d, J=8.0 Hz, ArH), 6.23 (1H, d, J=9.7 Hz, C=CH), 5.46 (1H, d, J=9.7 Hz, C=CH), 4.12 (2H, q, J=7.1 Hz, OCH_2), 3.64 (1H, br s (exchanges with D_2O), NH), 3.43 (2H, s, CH_2), 1.29 (6H, s, Me), 1.24 (3H, t, J=7.1 Hz, Me); *m/z* 246 (M+H, 80%), 245 (M, 20), 244 (M−H, 35), 230 (100), 202 (35), 172 (65), 157 (45).

4.2.9. 6-Iodo-2,2-dimethyl-1,2-dihydroquinoline 1i. (40%) as a light-sensitive orange oil; δ_H 7.19 (1H, d, J=2.0 Hz, ArH), 7.15 (1H, dd, J=2.0, 8.3 Hz, ArH), 6.19 (1H, d, J=8.3 Hz, ArH), 6.15 (1H, d, J=9.8 Hz, C=CH), 5.46 (1H, d, J=9.8 Hz, C=CH), 3.66 (1H, br s (exchanges with D_2O), NH), 1.29 (6H, s, Me); *m/z* 285 (M, 22%), 270 (100), 144 (90), 114 (10); HRMS: M, found 285.0024. $C_{11}H_{12}IN$ requires 285.0016.

4.2.10. Ethyl 2,2-dimethyl-1,2-dihydroquinoline-6-carboxylate 1j. (56%) as pale yellow prisms after crystallisation from ethanol/water, mp 106–107 °C; [Found: C, 72.6; H, 7.7; N, 6.0. $C_{14}H_{17}NO_2$ requires C, 72.7; H, 7.4; N, 6.1%]; ν_{max} ($CDCl_3$) 1690 cm^{-1}; δ_H 7.50 (2H, br s, ArH), 6.30 (1H, d, J=7.5 Hz, ArH), 6.20 (1H, d, J=9.5 Hz, C=C–H), 5.40 (1H, d, J=9.5 Hz, C=C–H), 4.30 (2H, q, J=7.2 Hz, CH_2), 3.45 (1H, br s, NH), 1.35 (3H, t, J=7.2 Hz, Me), 1.30 (6H, s, Me); *m/z* 231 (M, 50%).

4.2.11. Methyl 2,2-dimethyl-1-trifluoroacetyl-1,2-dihydroquinoline-6-carboxylate 6i and methyl 2,2-dimethyl-1,2-dihydroquinoline-6-carboxylate 1k. A mixture of the 6-iododihydroquinoline, **1i** (50 mg, 0.13 mmol), triphenylphosphine (100 mg, 0.39 mmol), triethylamine (37 µl, 0.26 mmol), methanol (0.5 mL) and dimethylformamide (1.5 mL) was purged with nitrogen for 10 min and then with carbon monoxide for 10 min. Palladium acetate (15 mg, 0.66 µmol) was added and the resulting mixture stirred at 100 °C under an atmosphere of carbon monoxide for 4 h. The reaction mixture was cooled and ether (5 mL) was added. Brine (5 mL) was added and the organic phase separated and combined with ethereal extracts of the aqueous phase. The combined organic extracts were washed with water (3×15 mL) and brine (2×15 mL), dried and the solvent removed. The residue was purified by flash chromatography; elution with light petroleum/ethyl acetate (80:20) provided the N-substituted ester, **6i**, (16 mg, 39%) as colourless needles, mp 92–94 °C; ν_{max} (CH_2Cl_2) 1690 cm^{-1}; δ_H 7.85 (1H, dd, J=2.0, 8.2 Hz, ArH), 7.78 (1H, d, J=2.0 Hz, ArH), 6.88 (1H, d, J=8.2 Hz, ArH), 6.45 (1H, d, J=9.7 Hz, C=CH), 5.81 (1H, d, J=9.7 Hz, C=CH), 3.92 (3H, s, OMe), 1.57 (6H, s, Me); *m/z* 313 (M, 5%), 298 (100), 170 (31), 157 (16), 115 (22); HRMS: M, found 313.0934. $C_{15}H_{14}F_3NO_3$ requires 313.0926.

Further elution gave the N-unsubstituted ester, **1k** (10 mg, 25%) as unstable tan prisms, mp 85–87 °C; ν_{max} ($CDCl_3$) 3400, 1705 cm^{-1}; δ_H 7.65 (1H, dd, J=1.9, 8.4 Hz, ArH), 7.55 (1H, d, J=1.9 Hz, ArH), 6.34 (1H, d, J=8.4 Hz, ArH), 6.26 (1H, d, J=9.8 Hz, C=CH), 5.46 (1H, dd, J=1.9, 9.8 Hz, C=CH), 4.13 (1H, br s (exchanges with D_2O), NH), 3.83 (3H, s, OMe), 1.33 (6H, s, Me); *m/z* 217 (M, 8%), 202 (100), 143 (20), 115 (10); HRMS: M, found 217.1092. $C_{13}H_{15}NO_2$ requires 217.1103.

4.2.12. 1-Acetyl-2,2,6-trimethyl-1,2-dihydroquinoline 3. To a stirred solution of 2,2,6-trimethyl-1,2-dihydroquinoline,[1,3] **1a**, (5.8 mmol) in pyridine (10 mL) and dichloromethane (10 mL) cooled to 0 °C was added acetyl chloride (8.7 mmol) dropwise. The resultant mixture was stirred under nitrogen at room temperature for 1 h. Water (10 mL) was added and the organic layer was separated and washed with hydrochloric acid (5%, 4×25 mL). The organic layer was dried and the solvent removed. The residue was purified by flash chromatography; elution with ethyl acetate/light petroleum yielded a yellow oil that crystallised on standing. Recrystallisation from ethanol/water afforded the acetamide, **3**, (1.00 g, 80%) as white needles, mp 67–68 °C; δ_H 6.50–7.05, (3H, m, ArH), 6.25 (1H, d, J=10 Hz, C=CH), 5.65 (1H, d, J=10 Hz, C=CH), 2.30 (3H, s, ArMe), 2.15 (3H, s, COMe), 1.55 (6H, s, Me); *m/z* 215 (M, 50%), 214 (25), 200 (10), 158 (50), 107 (100); HRMS: M, found 215.1301. $C_{14}H_{17}NO$ requires M, 215.1310.

4.3. General procedure for the synthesis of *N*-trifluoroacetyl dihydroquinolines

Trifluoroacetic anhydride (2.30 mmol) was added dropwise under an atmosphere of nitrogen to a solution of the corresponding dihydroquinoline (1.53 mmol) in dry dichloromethane (10 mL) and pyridine (0.5 mL) at 0 °C. The reaction was stirred at ambient temperature for 30–60 min, then quenched by the slow addition of water (10 mL). The organic phase was separated, washed with hydrochloric acid (10%, 3×15 mL) and water (15 mL), dried and the solvent removed. The residue was purified by flash chromatography; elution with light petroleum/ethyl acetate provided the *N*-trifluoroacetyldihydroquinolines. By this method, the following compounds were prepared:

4.3.1. 1-Trifluoroacetyl-2,2,6-trimethyl-1,2-dihydroquinoline 6a. (75%) as an orange oil; δ_H 6.96 (1H, dd, $J=1.5$, 8.0 Hz, ArH), 6.91 (1H, d, $J=1.5$ Hz, ArH), 6.76 (1H, d, $J=8.0$ Hz, ArH), 6.35 (1H, d, $J=9.7$ Hz, C=CH), 5.73 (1H, d, $J=9.7$ Hz, C=CH), 2.32 (3H, s, ArMe), 1.54 (6H, s, Me); *m/z* 269 (M, 5%), 254 (64), 172 (15), 157 (83), 156 (39), 115 (34), 69 (100); HRMS: M, found 269.1011. $C_{14}H_{14}F_3NO$ requires 269.1027.

4.3.2. 1-Trifluoroacetyl-6-methoxy-2,2-dimethyl-1,2-dihydroquinoline 6b. (43%) as an orange oil; δ_H 6.82 (1H, d, $J=8.4$ Hz, ArH), 6.68 (2H, m, ArH), 6.35 (1H, d, $J=9.7$ Hz, C=CH), 5.78 (1H, d, $J=9.7$ Hz, C=CH), 3.81 (3H, s, OMe), 1.55 (6H, s, Me); *m/z* 286 (M+H, 20%), 272 (100), 173 (55), 158 (15), 130 (15); HRMS: (M+H), found 286.1061. $C_{14}H_{15}F_3NO_2$ requires 286.1055.

4.3.3. 6-Bromo-1-trifluoroacetyl-2,2-dimethyl-1,2-dihydroquinoline 6c. (86%) as an orange oil; δ_H 7.2–7.3 (2H, m, ArH), 6.74 (1H, d, $J=8.4$ Hz, ArH), 6.33 (1H, d, $J=9.7$ Hz, C=CH), 5.81 (1H, d, $J=9.7$ Hz, C=CH), 1.55 (6H, s, Me); *m/z* 333/335 (M, 100), 221/223 (40), 170 (15); HRMS: M, found 332.9965. $C_{13}H_{11}BrF_3NO$ requires 332.9976.

4.3.4. 1-Trifluoroacetyl-6-hydroxy-2,2-dimethyl-1,2-dihydroquinoline 6d. (86%) as pale orange needles, mp 117–120 °C; ν_{max} ($CDCl_3$) 3150 cm^{-1}; δ_H 6.78 (1H, d, $J=8.6$ Hz, ArH), 6.64 (2H, m, ArH), 6.33 (1H, d, $J=9.7$ Hz, C=CH), 5.78 (1H, d, $J=9.7$ Hz, C=CH), 5.33 (1H, br s (exchanges with D_2O), OH), 1.55 (6H, s, Me); *m/z* 271 (M, 25%), 256 (100), 159 (50), 130 (15), 69 (25); HRMS: M, found 271.0810. $C_{13}H_{12}F_3NO_2$ requires 271.0820.

4.3.5. *N*-(2,2-Dimethyl-1-trifluoroacetyl-1,2-dihydro-6-quinolyl)acetamide 6e. (51%) as orange needles, mp 157–159 °C; ν_{max} ($CDCl_3$) 1670 cm^{-1}; δ_H 7.92 (1H, br s (exchanges with D_2O), NH), 7.51 (1H, d, $J=2.3$ Hz, ArH), 7.20 (1H, dd, $J=2.3$, 8.5 Hz, ArH), 6.81 (1H, d, $J=8.5$ Hz, ArH), 6.34 (1H, d, $J=9.7$ Hz, C=CH), 5.77 (1H, d, $J=9.7$ Hz, C=CH), 2.18 (3H, s, COMe), 1.54 (6H, s, Me); *m/z* 312 (M, 15%), 298 (100), 255 (15),158 (50); HRMS: M, found 312.1092. $C_{15}H_{15}F_3N_2O_2$ requires 312.1086.

4.3.6. 1-Trifluoroacetyl-2,2-dimethyl-1,2-dihydroquinoline 6f. (67%) as a pale orange oil; δ_H 7.14 (3H, m, ArH), 6.87 (1H, d, $J=7.3$ Hz, ArH), 6.40 (1H, d, $J=9.7$ Hz, C=CH), 5.76 (1H, d, $J=9.7$ Hz, C=CH), 1.56 (6H, s, Me); *m/z* 255 (M, 15%), 240 (100), 170 (15), 143 (35); HRMS: M, found 255.0865. $C_{13}H_{12}F_3NO$ requires 255.0871. (Attempted trifluoroacetylation of **1f** produced only the reduced compound, **6f**).

4.3.7. Ethyl 2-(2,2-dimethyl-1-trifluoroacetyl-1,2-dihydro-6-quinolyl)acetate 6g. (72%) as a yellow oil; ν_{max} ($CDCl_3$) 1720 cm^{-1}; δ_H 7.08 (2H, m, ArH), 6.82 (1H, d, $J=8.0$ Hz, ArH), 6.37 (1H, d, $J=9.7$ Hz, C=CH), 5.76 (1H, d, $J=9.7$ Hz, C=CH), 4.17 (2H, q, $J=7.1$ Hz, OCH_2), 3.58 (2H, s, CH_2), 1.55 (6H, s, Me), 1.27 (3H, t, $J=7.1$ Hz, Me); *m/z* 341 (M, 10%), 326 (100), 202 (40), 156 (60); HRMS: M, found 341.1227. $C_{17}H_{18}F_3NO_3$ requires 341.1239.

4.3.8. 1-Trifluoroacetyl-6-iodo-2,2-dimethyl-1,2-dihydroquinoline 6h. (75%) as a light-sensitive yellow oil; δ_H 7.48 (1H, dd, $J=2.0$, 8.3 Hz, ArH), 7.42 (1H, d, $J=2.0$ Hz, ArH), 6.61 (1H, d, $J=8.3$ Hz, ArH), 6.32 (1H, d, $J=9.7$ Hz, C=CH), 5.79 (1H, d, $J=9.7$ Hz, C=CH), 1.55 (6H, s, Me); *m/z* 381 (M, 15%), 366 (100), 269 (12), 240 (35), 170 (22); HRMS: M, found 380.9821. $C_{13}H_{11}F_3INO$ requires 380.9838.

4.4. General procedure for the preparation of 3,4-dichlorotetrahydroquinolines

A solution of chlorine in carbon tetrachloride (2.4 M, 0.83 mmol) was added dropwise under an atmosphere of nitrogen to a stirred solution of the corresponding dihydroquinoline (0.67 mmol) in dry dichloromethane (5 mL) and the mixture stirred at ambient temperature for 15–30 min. The solvent and excess chlorine were removed under reduced pressure and the residue purified by flash chromatography; elution with light petroleum/ethyl acetate gave the 3,4-dichloro compounds as unstable solids or oils. By this method, the following compounds were prepared.

4.4.1. 1-Acetyl-3,4-dichloro-2,2,6-trimethyl-1,2,3,4-tetrahydroquinoline 4. (75%) as an unstable viscous yellow liquid; δ_H 6.80–7.35 (3H, m, ArH), 5.20 (1H, d, $J=5.5$ Hz, CHCl), 4.50 (1H, d, $J=5.5$ Hz, CHCl), 2.40 (3H, s, ArMe), 2.10 (3H, s, COMe), 1.85 (3H, s, Me), 1.40 (3H, s, Me); *m/z* 285/287/289 (M, 30%), 250/252/254 (30), 243/245/247 (30), HRMS: M, found 285.0675. $C_{14}H_{17}NOCl_2$ requires 285.0689.

4.4.2. 1-Acetyl-3,4,8-trichloro-2,2,6-trimethyl-1,2,3,4-tetrahydroquinoline 5. Obtained from the same reaction. (0.17 g, 13%) as a slightly impure yellow oil; δ_H 6.90–7.15, (2H, m, ArH), 5.10 (1H, d, $J=4.5$ Hz, CHCl), 4.70 (1H, d, $J=4.5$ Hz, CHCl), 2.40 (3H, s, ArMe), 2.05 (3H, s, COMe), 2.00 (6H, s, Me); *m/z* 321/323/325 (M, 15%).

4.4.3. 3,4-Dichloro-1-trifluoroacetyl-6-methoxy-2,2-dimethyl-1,2,3,4-tetrahydroquinoline 7b. (88%) as an unstable yellow oil; δ_H 7.04 (1H, d, $J=2.8$ Hz, ArH), 6.94 (1H, d, $J=8.8$ Hz, ArH), 6.88 (1H, dd, $J=2.8$, 8.8 Hz, ArH), 4.47 (1H, d, $J=4.5$ Hz, CHCl), 5.19 (1H, d, $J=4.5$ Hz, CHCl), 3.84 (3H, s, OMe), 1.81 (3H, s, Me), 1.51 (3H, s, Me); *m/z* 355/357/359 (M, 100%), 322/324/326 (70), 280/282 (100), 272 (50), 230 (55), 188 (55); HRMS: M, found 355.0343. $C_{14}H_{14}Cl_2F_3NO_2$ requires 355.0354.

4.4.4. 6-Bromo-3,4-dichloro-1-trifluoroacetyl-2,2-dimethyl-1,2,3,4-tetrahydroquinoline 7c. (90%) as an unstable pale yellow oil; δ_H 7.48 (1H, dd, $J=2.1$, 8.3 Hz, ArH), 6.85 (1H, d, $J=8.3$ Hz, ArH), 6.68 (1H, d, $J=2.1$ Hz, ArH, 5.21 (1H, d, $J=4.4$ Hz, CHCl), 4.44 (1H, d, $J=4.4$ Hz, CHCl), 1.77 (3H, s, Me), 1.56 (3H, s, Me); *m/z* 403/405/407 (M, 40%), 368/370/372 (100), 247 (60); HRMS: M, found 402.9334. $C_{13}H_{11}BrCl_2F_3NO$ requires 402.9353.)

4.4.5. 3,4-Dichloro-1-trifluoroacetyl-6-hydroxy-2,2-dimethyl-1,2,3,4-tetrahydroquinoline 7d. (100%) as unstable pale yellow needles, mp 100–102 °C; ν_{max} ($CDCl_3$) 3160 cm^{-1}; δ_H 7.03 (1H, d, $J=2.6$ Hz, ArH), 6.90 (1H, d, $J=8.6$ Hz, ArH), 6.84 (1H, dd, $J=2.6$, 8.6 Hz, ArH), 6.25 (1H, br s (exchanges with D_2O), OH), 5.16 (1H,

d, J=4.6 Hz, CHCl), 4.45 (1H, d, J=4.6 Hz, CHCl), 1.81 (3H, s, Me), 1.53 (3H, s, Me); *m/z* 341/343/345 (M, 100%), 306 (75), 266 (30), 264 (90), 216 (60), 174 (90).

4.4.6. *N*-(3,4-Dichloro-2,2-dimethyl-1-trifluoroacetyl-1,2,3,4-tetrahydro-6-quinolyl)acetamide 7e. (75%) as unstable pale yellow needles, mp 145–147 °C; ν_{max} ($CDCl_3$) 1670 cm^{-1}; δ_H 8.14 (1H, br s (exchanges with D_2O), NH), 7.84 (1H, d, J=2.2 Hz, ArH), 7.52 (1H, dd, J=2.2, 8.7 Hz, ArH), 6.93 (1H, d, J=8.7 Hz, ArH), 5.20 (1H, d, J=4.4 Hz, CHCl), 4.46 (1H, d, J=4.4 Hz, CHCl), 2.20 (3H, s, COMe), 1.79 (3H, s, Me), 1.53 (3H, s, Me); *m/z* 382/384/386 (M, 100%), 347/349 (75), 312 (100), 305/307 (90), 297 (100); HRMS: M, found 382.0476. $C_{15}H_{15}Cl_2F_3N_2O_2$ requires 382.0463.

4.4.7. 3,4-Dichloro-1-trifluoroacetyl-2,2-dimethyl-1,2,3,4-tetrahydroquinoline 7f. (83%) as an unstable yellow oil; δ_H 7.54 (1H, dd, J=3.7, 5.8 Hz, ArH), 7.36 (2H, m, ArH), 6.98 (1H, m, ArH), 5.27 (1H, d, J=4.5 Hz, CHCl), 4.48 (1H, d, J=4.5 Hz, CHCl), 1.80 (3H, s, Me), 1.55 (3H, s, Me); *m/z* 325/327/329 (M, 25%), 290/292 (100), 253 (20), 239 (40); HRMS: M, found 325.0245. $C_{13}H_{12}Cl_2F_3NO$ requires 325.0248.

4.4.8. Ethyl 2-(3,4-dichloro-1-trifluoroacetyl-2,2-dimethyl-1,2,3,4-tetrahydro-6-quinolyl)acetate 7g. (92%) as an unstable yellow oil; ν_{max} ($CDCl_3$) 1720 cm^{-1}; δ_H 7.48 (1H, d, J=1.8 Hz, ArH), 7.28 (1H, dd, J=1.8, 8.0 Hz, ArH), 6.93 (1H, d, J=8.0 Hz, ArH), 5.25 (1H, d, J=4.5 Hz, CHCl), 4.45 (1H, d, J=4.5 Hz, CHCl), 4.18 (2H, q, J=7.0 Hz, OCH_2), 3.65 (2H, s, CH_2), 1.78 (3H, s, Me), 1.55 (3H, s, Me), 1.27 (3H, t, J=7.0 Hz, Me); *m/z* 411/413/415 (M, 35%), 376/378 (100), 340 (25), 326 (55), 260 (40); HRMS: M, found 411.0596. $C_{17}H_{18}Cl_2F_3NO_3$ requires 411.0616.

4.4.9. 3,4-Dichloro-1-trifluoroacetyl-6-iodo-2,2-dimethyl-1,2,3,4-tetrahydroquinoline 7h. (68%) as unstable white prisms, mp 75–77 °C; δ_H 7.86 (1H, d, J=1.9 Hz, ArH), 7.66 (1H, dd, J=1.9, 8.4 Hz, ArH), 6.70 (1H, d, J=8.4 Hz, ArH), 5.19 (1H, d, J=4.4 Hz, CHCl), 4.43 (1H, d, J=4.4 Hz, CHCl), 1.77 (3H, s, Me), 1.56 (3H, s, Me); *m/z* 451/453/455 (M, 60%), 416/418 (55), 368 (22), 290 (26), 247 (22), 69 (100).

4.4.10. Methyl 3,4-dichloro-2,2-dimethyl-1-trifluoroacetyl-1,2,3,4-tetrahydroquinoline-6-carboxylate 7i. (80%) as unstable yellow prisms, mp 104–106 °C; ν_{max} ($CDCl_3$) 1695 cm^{-1}; δ_H 8.23 (1H, d, J=1.9 Hz, ArH), 8.02 (1H, dd, J=1.9, 8.3 Hz, ArH), 6.99 (1H, d, J=8.3 Hz, ArH), 5.32 (1H, d, J=4.3 Hz, CHCl), 4.48 (1H, d, J=4.3 Hz, CHCl), 3.95 (3H, s, OMe), 1.77 (3H, s, Me), 1.59 (3H, s, Me); *m/z* 383/385/387 (M, 22%), 348/350 (100), 312 (13), 298 (20), 258 (16), 216 (15); HRMS: M, found 383.0303. $C_{15}H_{14}Cl_2F_3NO_3$ requires 383.0303.

4.4.11. 3,4-Dichloro-2,2,6-trimethyl-1,2,3,4-tetrahydroquinoline 10. A solution of chlorine in carbon tetrachloride (2.4 M, 0.18 mL, 0.43 mmol) was added dropwise to a stirred solution of the dihydroquinoline, **1a**, (0.05 g, 0.29 mmol) in concentrated hydrochloric acid (5 mL) and the resulting mixture stirred vigorously at room temperature for 30 min. The mixture was neutralised with sodium hydroxide solution (10%) and extracted with dichloromethane (3×10 mL). The combined organic extracts were dried and the solvent removed. The residue was purified by flash chromatography; elution with light petroleum/ethyl acetate (85:15) gave the dichloro compound, **10**, (33 mg, 47%) as unstable white prisms, mp 107–109 °C; δ_H 7.25 (1H, d, J=1.5 Hz, ArH), 6.92 (1H, dd, J=1.5, 8.1 Hz, ArH), 6.49 (1H, d, J=8.1 Hz, ArH), 4.76 (1H, d, J=9.2 Hz, CHCl), 3.98 (1H, d, J=9.2 Hz, CHCl), 2.60 (1H, br s (exchanges with D_2O), NH), 2.25 (3H, s, ArMe), 1.39 (3H, s, Me), 1.24 (3H, s, Me); *m/z* 243/245/247 (M, 1%), 208/210 (25), 192/194 (100).

4.4.12. 1-Acetyl-3-chloro-2,2,6-trimethyl-1,2,3,4-tetrahydroquinolin-4-ol 11. A solution of chlorine in carbon tetrachloride (2.4 M, 0.15 mL, 0.35 mmol) was added dropwise to a solution of the dihydroquinoline, **3**, (50 mg, 0.23 mmol) in tetrahydrofuran (2 mL) and water (2 mL) and the resulting mixture stirred vigorously under an atmosphere of nitrogen for 24 h. Water (5 mL) was added and the mixture extracted with dichloromethane (3×10 mL). The combined organic extracts were dried and the solvent removed. The residue was purified by flash chromatography; elution with light petroleum/ethyl acetate (1:1) provided the chlorohydrin, **11**, (60 mg, 96%) as cream prisms, mp 139–141 °C; ν_{max} ($CDCl_3$) 3575 cm^{-1}; δ_H 7.39 (1H, d, J=1.8 Hz, ArH), 7.07 (1H, dd, J=1.8, 8.1 Hz, ArH), 6.84 (1H, d, J=8.1 Hz, ArH), 4.71 (1H, dd, J=3.0, 9.5 Hz, C*H*OH), 3.67 (1H, d, J=9.5 Hz, CHCl), 2.84 (1H, br s (exchanges with D_2O), OH), 2.37 (3H, s, ArMe), 2.11 (3H, s, COMe), 1.69 (3H, s, Me), 1.68 (3H, s, Me); *m/z* 267/269 (M, 44%), 225/227 (60), 210/212 (100), 198 (46); HRMS: M, found 267.1018. $C_{14}H_{18}ClNO_2$ requires 267.1026.)

This compound also formed slowly from the dichloride, **4**, if it was left exposed to the atmosphere.

4.4.13. 3-Chloro-1-trifluoroacetyl-2,2,6-trimethyl-1,2,3,4-tetrahydroquinolin-4-ol 13, and 1-trifluoroacetyl-3,4-dichloro-1,2,3,4-tetrahydroquinoline 7a. The chlorohydrin, **13**, was prepared, from **6a**, in a similar manner (43 mg, 36%) as a pale yellow gum; ν_{max} ($CDCl_3$) 3595 cm^{-1}; δ_H 7.43 (1H, d, J=1.6 Hz, ArH), 7.11 (1H, dd, J=1.6, 8.4 Hz, ArH), 6.89 (1H, d, J=8.4 Hz, ArH), 4.74 (1H, d, J=9.2 Hz, C*H*OH), 3.69 (1H, d, J=9.2 Hz, CHCl), 2.85 (1H, br s (exchanges with D_2O), OH), 2.39 (3H, s, ArMe), 1.68 (3H, s, Me), 1.67 (3H, s, Me); *m/z* 321/323 (M, 100%), 244 (54), 216 (45), 203 (63), 162 (86); HRMS: M, found 321.0733. $C_{14}H_{15}ClF_3NO_2$ requires 321.0743.)

4.4.14. 7a. Also obtained from this reaction was the dichloride. (59 mg, 47%) as a pale yellow oil; δ_H 7.33 (1H, d, J=1.5 Hz, ArH), 7.14 (1H, dd, J=1.5, 8.3 Hz, ArH), 6.87 (1H, d, J=8.3 Hz, ArH), 5.22 (1H, d, J=4.4 Hz, CHCl), 4.47 (1H, d, J=4.4 Hz, CHCl). 2.38 (3H, s, ArMe), 1.79 (3H, s, Me), 1.52 (3H, s, Me); *m/z* 339/341/343 (M, 32%), 304/306 (77), 262 (45), 214 (34), 172 (50), 69 (100); HRMS: M, found 339.0402. $C_{14}H_{14}Cl_2F_3NO$ requires 339.0404.)

4.4.15. 1-Acetyl-3,4-dibromo-2,2,6-trimethyl-1,2,3,4-tetrahydroquinoline 12. Bromine (0.44 g, 2.7 mmol) was

added dropwise to a stirred solution of the dihydroquinoline, **3**, (0.59 g, 2.7 mmol) in dry dichloromethane (5 mL) and the resulting mixture stirred at ambient temperature for 1 h. The solvent and excess bromine were removed under reduced pressure and the residue purified by flash chromatography; elution with light petroleum/ethyl acetate (60:40) provided the dibromo compound, **12**, (0.94 g, 91%) as an unstable orange oil; δ_H 7.23 (1H, d, $J=1.7$ Hz, ArH), 7.11 (1H, dd, $J=1.7$, 8.2 Hz, ArH), 6.90 (1H, d, $J=8.2$ Hz, ArH), 5.55 (1H, d, $J=3.9$ Hz, CHBr), 4.89 (1H, d, $J=3.9$ Hz, CHBr), 2.36 (3H, s, COMe), 2.10 (3H, s, ArMe), 1.91 (3H, s, Me), 1.37 (3H, s, Me); *m/z* 373/375/377 (M, 2%), 314/316/318 (25), 294/296 (10), 236/238 (15), 200 (20), 158 (100).

4.5. General procedure for the synthesis of 3-chloro-tetrahydroquinolines

Sodium cyanoborohydride (1.75 mmol) was added to a solution of freshly dried zinc chloride[18] (0.87 mmol) in dry ether (10 mL) and the mixture stirred at ambient temperature under an atmosphere of nitrogen for 20 min. A solution of the dichlorotetrahydroquinoline (0.87 mmol) in dry ether (4 mL) was then added under an atmosphere of nitrogen and the resulting mixture stirred at ambient temperature for 3–10 days. The reaction was quenched with saturated sodium bicarbonate solution (15 mL), the organic phase separated and washed with water (15 mL) and brine (3× 15 mL), dried and the solvent removed. The residue was purified by flash chromatography; elution with light petroleum/ethyl acetate provided the 3-chloro compounds. By this method, the following compounds were prepared.

4.5.1. 1-Acetyl-3-chloro-2,2,6-trimethyl-1,2,3,4-tetrahydroquinoline. As white plates after crystallisation from light petroleum (0.26 g, 65%), mp 74–76 °C; [Found: C, 67.0; H, 7.5; N, 5.6. $C_{14}H_{18}NOCl$ requires C, 66.9; H, 7.2; N, 5.6%.]; δ_H 6.96–7.02 (2H, m, ArH), 6.85 (1H, d, $J=8$ Hz, ArH), 4.15 (1H, dd, $J=3.4$, 6.7 Hz, CHCl), 3.15 (1H, dd, $J=3.4$, 15.3 Hz, 1H of CH_2), 3.01 (1H, dd, $J=6.7$, 15.3 Hz, 1H of CH_2–), 2.33 (3H, s, ArMe),2.11 (3H, s, COMe), 1.68 (6H, s, Me); *m/z* 251/253 (M, 60%), 9/211 (70), 196 (75), 194 (100).

4.5.2. 3-Chloro-2,2-dimethyl-6-methoxy-1-trifluoroacetyl-1,2,3,4-tetrahydroquinoline 14b. (78%) as a pale yellow oil; δ_H 6.93 (1H, d, $J=8.8$ Hz, ArH), 6.75 (2H, m, ArH), 4.17 (1H, dd, $J=3.6$, 6.3 Hz, CHCl), 3.81 (3H, s, OMe), 3.19 (1H, dd, $J=3.6$, 15.3 Hz, 1H of CH_2), 3.05 (1H, dd, $J=6.3$, 15.3 Hz, 1H of CH_2), 1.66 (6H, s, Me); *m/z* 321/323 (M, 60%), 286 (15), 270 (10), 244 (100), 232 (25), 188 (15); HRMS: M, found 321.0749. $C_{14}H_{15}ClF_3NO_2$ requires 321.0743.

4.5.3. 6-Bromo-3-chloro-2,2-dimethyl-1-trifluoroacetyl-1,2,3,4-tetrahydroquinoline 14c. (20%) as white needles, mp 78–80 °C; [Found: C, 42.5; H, 3.3; N, 3.7. $C_{13}H_{12}BrClF_3NO$ requires C, 42.1; H, 3.3; N, 3.8%]; δ_H 7.37 (2H, m, ArH), 6.86 (1H, dd, $J=0.8$, 8.9 Hz, ArH), 4.21 (1H, dd, $J=3.5$, 5.8 Hz, CHCl), 3.24 (1H, dd, $J=3.5$, 15.8 Hz, 1H of CH_2), 3.09 (1H, dd, $J=5.8$, 15.8 Hz, 1H of CH_2), 1.67 (3H, s, Me), 1.63 (3H, s, Me); *m/z* 369/371/373 (M, 50%), 292/294 (75), 279/281 (25), 213 (100).

4.5.4. 3-Chloro-2,2-dimethyl-6-hydroxy-1-trifluoroacetyl-1,2,3,4-tetrahydroquinoline 14d. (88%) as a white powder, mp 118–119 °C; [Found: C, 50.5; H, 4.1; N, 4.7. $C_{13}H_{13}ClF_3NO_2$ requires C, 50.7; H, 4.3; N, 4.6%]; ν_{max} ($CDCl_3$) 3155 cm^{-1}; δ_H 6.89 (1H, d, $J=8.3$ Hz, ArH), 6.73 (1H, dd, $J=2.7$, 8.3 Hz, ArH), 6.70 (1H, d, $J=2.7$ Hz, ArH), 5.91 (1H, br s (exchanges with D_2O), OH), 4.18 (1H, dd, $J=3.5$, 6.2 Hz, CHCl), 3.17 (1H, dd, $J=3.5$, 15.4 Hz, 1H of CH_2), 3.04 (1H, dd, $J=6.2$, 15.4 Hz, 1H of CH_2), 1.67 (3H, s, Me), 1.65 (3H, s, Me); *m/z* 307/309 (M, 30%), 272 (5), 230 (100), 218 (25), 174 (12).

4.5.5. *N*-(3-Chloro-2,2-dimethyl-1-trifluoroacetyl-1,2,3,4-tetrahydro-6-quinolyl)acetamide 14e. (55%) as pale yellow prisms, mp 146–148 °C; [Found: C, 51.4; H, 4.5; N, 7.7. $C_{15}H_{16}ClF_3N_2O_2$ requires C, 51.6; H, 4.6; N, 8.0%]; ν_{max} ($CDCl_3$) 1675 cm^{-1}; δ_H 7.78 (1H, br s (exchanges with D_2O), NH), 7.65 (1H, d, $J=2.3$ Hz, ArH), 7.26 (1H, dd, $J=2.3$, 8.6 Hz, ArH), 6.93 (1H, d, $J=8.6$ Hz, ArH), 4.19 (1H, dd, $J=3.5$, 5.9 Hz, CHCl), 3.21 (1H, dd, $J=3.5$, 15.6 Hz, 1H of CH_2), 3.07 (1H, dd, $J=5.9$, 15.6 Hz, 1H of CH_2), 2.19 (3H, s, COMe), 1.67 (3H, s, Me), 1.63 (3H, s, Me); *m/z* 348/350 (M, 35%), 313 (5), 271 (60), 254 (45), 223 (100).

4.5.6. 3-Chloro-2,2-dimethyl-1-trifluoroacetyl-1,2,3,4-tetrahydroquinoline 14f. (66%) as colourless prisms, mp 40–42 °C; [Found: C, 53.8; H, 4.4; N, 4.7. $C_{13}H_{13}ClF_3NO$ requires C, 53.5; H, 4.5; N, 4.8%]; δ_H 7.24 (2H, m, ArH), 6.99 (2H, m, ArH), 4.19 (1H, dd, $J=3.6$, 6.3 Hz, CHCl), 3.25 (1H, dd, $J=3.6$, 15.5 Hz, 1H of CH_2), 3.12 (1H, dd, $J=6.3$, 15.5 Hz, 1H of CH_2), 1.68 (3H, s, Me), 1.65 (3H, s, Me); *m/z* 291/293 (M, 20%), 256 (5), 240 (10), 214 (100), 202 (25), 158 (15).

4.5.7. Ethyl 2-(3-chloro-2,2-dimethyl-1-trifluoroacetyl-1,2,3,4-tetrahydro-6-quinolyl)acetate 14g. (76%) as a viscous, pale yellow oil; ν_{max} ($CDCl_3$) 1720 cm^{-1}; δ_H 7.15 (2H, m, ArH), 6.94 (1H, br s (not exchangeable with D_2O), ArH), 4.17 (3H, m, CHCl and OCH_2), 3.61 (2H, s, $ArCH_2$), 3.23 (1H, dd, $J=6.4$, 15.6 Hz, 1H of CH_2), 3.11 (1H, dd, $J=3.7$, 15.6 Hz, 1H of CH_2), 1.67 (3H, s, Me), 1.64 (3H, s, Me), 1.26 (3H, t, $J=7.2$ Hz, Me); *m/z* 378/380 (M+H, 35%), 342 (7), 300 (20), 288 (25), 226 (100); HRMS: M, found 377.0994. $C_{17}H_{19}ClF_3NO_3$ requires 377.1005.)

4.5.8. 3-Chloro-2,2-dimethyl-6-iodo-1-trifluoroacetyl-1,2,3,4-tetrahydroquinoline 14h. (33%) as a viscous, pale yellow oil; δ_H 7.56 (1H, br s (not exchangeable with D_2O), ArH), 7.24 (1H, m, ArH), 6.72 (1H, d, $J=8.8$ Hz, ArH), 4.19 (1H, dd, $J=3.6$, 5.8 Hz, CHCl), 3.22 (1H, dd, $J=3.6$, 15.8 Hz, 1H of CH_2), 3.07 (1H, dd, $J=5.8$, 15.8 Hz, 1H of CH_2), 1.67 (3H, s, Me), 1.62 (3H, s, Me); *m/z* 417/419 (M, 40%), 382 (5), 340 (40), 291 (20), 258 (25), 214 (85), 69 (100); HRMS: M, found 416.9585. $C_{13}H_{12}ClF_3INO$ requires 416.9606.

4.5.9. Methyl 3-chloro-2,2-dimethyl-1-trifluoroacetyl-1,2,3,4-tetrahydroquinoline-6-carboxylate 14i. (34%) as a colourless oil; ν_{max} (CH_2Cl_2) 1690 cm^{-1}; δ_H 7.92 (2H, m, ArH); 7.02 (1H, d, $J=7.9$ Hz, ArH), 3.93 (3H, s, OMe), 4.24 (1H, dd, $J=3.7$, 5.6 Hz, CHCl), 3.19 (1H, dd, $J=3.7$, 16.0 Hz, 1H of CH_2), 3.13 (1H, dd, $J=5.6$, 16.0 Hz, 1H of CH_2), 1.69 (3H, s, Me), 1.63 (3H, s, Me); *m/z* 349/351

(M, 38%), 272 (100), 260 (49), 240 (20), 228 (42); HRMS: M, found 349.0692. $C_{15}H_{15}ClF_3NO_3$ requires 349.0693.)

4.5.10. 3,4-Epoxy-1-trifluoroacetyl-2,2,6-trimethyl-1,2,3,4-tetrahydroquinoline 15. Sodium bicarbonate (255 mg, 3.0 mmol) and *m*-chloroperoxybenzoic acid (80%, 0.55 g, 2.4 mmol) were added to a solution of the dihydroquinoline, **6a**, (0.50 g, 1.9 mmol) in dichloromethane (25 mL) and the resulting mixture stirred under an atmosphere of nitrogen for 41 h. The mixture was diluted with dichloromethane (10 mL), washed with saturated sodium bicarbonate solution (3×15 mL) and water (2×15 mL), dried and the solvent removed. The residue was purified by flash chromatography; elution with light petroleum/ethyl acetate (70:30) afforded the epoxide, **15**, (0.39 g, 74%) as a pale orange oil; δ_H 7.26 (1H, d, J=1.8 Hz, ArH), 7.12, (1H, dd, J=1.8, 8.1 Hz, ArH), 6.77 (1H, d, J=8.1 Hz, ArH), 3.86 (1H, d, J=4.2 Hz, CHO), 3.41 (1H, d, J=4.2 Hz, CHO), 2.37 (3H, s, ArMe), 1.88 (3H, s, Me), 1.21 (3H, s, Me); *m*/*z* 285 (M, 46%), 214 (100), 145 (29), 144 (28), 69 (48); HRMS: M, found 285.0980. $C_{14}H_{14}F_3NO_2$ requires 285.0977.

4.5.11. 1-Trifluoroacetyl-2,2,6-trimethyl-1,2,3,4-tetrahydroquinolin-3-ol 16. A solution of the epoxide, **15**, (0.39 g, 1.4 mmol) in ethyl acetate (10 mL) was stirred with 5% palladium on carbon (100 mg) under an atmosphere of hydrogen for 23 h. The mixture was filtered through a pad of celite and the solvent removed. The residue was purified by flash chromatography; elution with light petroleum/ethyl acetate (1:1) provided the alcohol, **16**, (0.27 g, 69%) as a colourless, unstable oil ν_{max} ($CDCl_3$) 3600 cm^{-1}; δ_H 7.04 (2H, m, ArH), 6.91 (1H, d, J=7.9 Hz, ArH), 3.89 (1H, m, C*H*OH), 2.82 (1H, dd, J=5.5, 14.4 Hz, 1H of CH_2), 2.94 (1H, dd, J=2.4, 14.4 Hz, 1H of CH_2), 2.35 (3H, s, ArMe), 1.59 (3H, s, Me), 1.56 (3H, s, Me), 1.43 (1H, d, J=7.8 Hz (exchanges with D_2O), OH); *m*/*z* 287 (M, 84%), 271 (48), 217 (25), 216 (30), 190 (35), 158 (100); HRMS: M, found 287.1123. $C_{14}H_{16}F_3NO_2$ requires 287.1133.

4.5.12. 1-Trifluoroacetyl-2,2,6-trimethyl-1,2,3,4-tetrahydro-3-quinolone 17. Jones reagent was added dropwise to a solution of the alcohol, **16**, (10 mg, 35 μmol) in acetone (5 mL) until the orange colour just persisted. Water (5 mL) was added and the mixture extracted with dichloromethane (3×10 mL). The combined organic extracts were dried and the solvent removed. The residue was purified by flash chromatography; elution with light petroleum/ethyl acetate (80:20) afforded the ketone, **17**, (7.3 mg, 74%) as a pale yellow oil; ν_{max} ($CDCl_3$) 1730 cm^{-1}; δ_H (acquired at 0 °C) 7.11 (2H, m, ArH), 7.01 (1H, d, J=8.0 Hz, ArH), 3.87 (1H, d, J=13.8 Hz, 1H of CH_2), 3.36 (1H, d, J=13.8 Hz, 1H of CH_2), 2.31 (3H, s, ArMe), 1.79 (3H, s, Me), 1.34 (3H, s, Me); *m*/*z* 285 (M, 30%), 257 (60), 242 (58), 188 (50), 160 (90), 145 (100); HRMS: M, found 285.0970. $C_{14}H_{14}F_3NO_2$ requires 285.0977.

4.5.13. 2,2,6-Trimethyl-1,2,3,4-tetrahydro-3-quinolyl trifluoroacetate 18. The alcohol, **16**, (100 mg, 0.35 mmol) and triphenylphosphine (270 mg, 1.1 mmol) were dissolved in dry tetrahydrofuran (5 mL) under an atmosphere of nitrogen. Anhydrous zinc chloride (48 mg, 0.35 mmol) in dry tetrahydrofuran (1 mL) and diethyl azodicarboxylate (0.18 g, 1.1 mmol) in dry tetrahydrofuran (1 mL) were added consecutively with stirring. The resulting mixture was stirred under an atmosphere of nitrogen for 2 h, the solvent removed in vacuo and the residue purified by flash chromatography; elution with light petroleum/ethyl acetate (80:20) gave the trifluoroacetate, **18**, (78 mg, 78%) as an unstable pale yellow oil; ν_{max} ($CDCl_3$) 1780 cm^{-1}; δ_H 6.84 (1H, d, J=8.1 Hz, ArH), 6.81 (1H, s, ArH), 6.46 (1H, d, J=8.1 Hz, ArH), 5.10 (1H, dd, J=5.5, 7.4 Hz, CHO), 3.56 (1H, br s (exchanges with D_2O), NH), 2.86 (1H, dd, J=7.4, 16.9 Hz, 1H of CH_2), 2.22, (3H, s, ArMe), 1.22 (3H, s, Me), 1.20 (3H, s, Me); *m*/*z* 287 (M, 9%), 272 (7), 173 (26), 158 (100), 132 (41).

Other attempts at the above reaction using the same conditions but replacing the zinc chloride with either tetrabutylammonium chloride or tetrabutylammonium bromide also gave the trifluoroacetate, **18**, as the sole product.

4.5.14. 2,2,6-Trimethyl-1,2,3,4-tetrahydroquinolin-3-ol 19. An aqueous solution of potassium bicarbonate (10%, 2.5 mL, 2.4 mmol) was added dropwise to a solution of the trifluoroacetate, **18**, (77 mg, 0.27 mmol) in methanol (5 mL) and the resulting mixture stirred at room temperature under an atmosphere of nitrogen for 40 min. Water (5 mL) was added and the mixture extracted with dichloromethane (3×10 mL). The combined organic extracts were dried and the solvent removed. The residue was purified by flash chromatography; elution with light petroleum/ethyl acetate (60:40) provided the aminoalcohol, **19**, (40 mg, 78%) as cream prisms, mp 73–74 °C; ν_{max} ($CDCl_3$) 3500, 3370 cm^{-1}; δ_H 6.81 (2H, m, ArH), 6.43 (1H, d, J=8.7 Hz, ArH), 3.63 (1H, t, J=4.4 Hz, C*H*OH), 3.46, (1H, br s (exchanges with D_2O), NH), 2.99 (1H, dd, J=4.4, 17.0 Hz, 1H of CH_2), 2.71 (1H, dd, J=4.4, 17.0 Hz, 1H of CH_2), 2.21 (3H, s, ArMe), 2.18 (1H, br s (exchanges with D_2O), OH), 1.20 (3H, s, Me), 1.11 (3H, s, Me); *m*/*z* 191 (M, 69%), 176 (100), 158 (31), 146 (34), 132 (36); HRMS: M, found 191.1314. $C_{12}H_{17}NO$ requires 191.1310.

4.5.15. 3-Chloro-2,2,6-trimethyl-1,2,3,4-tetrahydroquinoline 20. A mixture of the trifluoroacetate, **18**, (20 mg, 0.07 μmol), tetrabutylammonium chloride (28 mg, 0.10 mmol) and tetrahydrofuran (5 mL) was refluxed for 24 h. The reaction mixture was cooled, diluted with dichloromethane (5 mL), washed with water (2×10 mL) and brine (5 mL), dried and the solvent removed. The residue was purified by flash chromatography; elution with light petroleum/ethyl acetate (60:40) gave an inseparable mixture of the starting trifluoroacetate, **18**, and the 3-chloro compound, **20**, (6.5 mg); spectroscopic data for **20**; δ_H 6.83 (2H, m, ArH), 6.45 (1H, d, J=8.0 Hz, ArH), 4.08 (1H, dd, J=5.4, 8.4 Hz, CHCl), 3.60 (1H, br s (exchanges with D_2O), NH), 3.23 (1H, dd, J=5.4, 16.9 Hz, 1H of CH_2), 3.03 (1H, dd, J=8.4, 16.9 Hz, 1H of CH_2), 2.21 (3H, s, ArMe), 1.30 (3H, s, Me), 1.25 (3H, s, Me); *m*/*z* 209/211 (M, 29%), 194 (1), 174 (1), 158 (2).

4.5.16. 1-Acetyl-2,2,6-trimethyl-1,2,3,4-tetrahydroquinoline-4-ol 21. To a stirred solution of mercuric acetate (0.15 g, 0.5 mmol) in water (1 mL) was added tetrahydrofuran (1 mL); the resulting suspension was vigorously stirred and then the acetamide, **3**, (0.10 g, 0.5 mmol) was

added and the resultant mixture was stirred at room temperature for 24 h. Sodium hydroxide (3.0 M, 0.5 mL) was added followed by a solution of sodium borohydride (0.5 M) in sodium hydroxide (3.0 M, 0.5 mL). After 45 min the organic layer was separated and combined with dichloromethane extracts of the aqueous phase. The combined organic extracts were dried and the solvent removed. The residue was purified by flash chromatography; elution with ethyl acetate/light petroleum (1:1) afforded an orange oil that solidified on standing. Recrystallisation of this solid from dichloromethane/light petroleum yielded the alcohol, **21**, (0.018 g, 15%) as cream-coloured prisms, mp 123–125 °C; ν_{max} ($CDCl_3$) 3550 cm^{-1}; δ_H 7.27 (1H, br s, ArH), 7.01, (1H, d, J=7.9 Hz, ArH), 6.83 (1H, d, J=7.9 Hz, ArH), 4.76 (1H, br d, J=11.2 Hz, CHO), 2.10–2.40 (2H, m, CH_2), 2.37 (3H, s, ArMe), 2.10 (3H, s, COMe), 1.73 (3H, s, Me), 1.53 (3H, s, Me), 1.46 (1H, br s, OH); *m/z* 233 (M, 50%), 217 (10), 176 (100), 158 (95); HRMS: M, Found 233.1426. $C_{14}H_{19}NO_2$ requires 233.1416.

4.5.17. 1-Acetyl-2,2,6-trimethyl-1,2,3,4-tetrahydroquinoline-4-one 22. A solution of chromium trioxide in sulfuric acid (30%, 0.014 mL, 0.04 mmol) was added to a stirred solution of the alcohol, **21**, (0.01 g, 0.04 mmol) in acetone (2 mL) and the mixture was stirred under nitrogen for 2 h. Water (3 mL) was then added and the mixture was extracted with dichloromethane (3×5 mL). The combined organic extracts were dried and the solvent removed. The residue was purified by flash chromatography; elution with ethyl acetate/light petroleum (1:1) yielded the ketone, **22**, (7 mg, 71%) as a yellow oil; ν_{max} ($CDCl_3$) 1710 cm^{-1}; δ_H 7.75 (1H, d, J=2.0 Hz, ArH), 7.25 (1H, dd, J=2.0, 8.2 Hz, ArH), 6.80 (1H, d, J=8.2 Hz, ArH), 2.70 (2H, s, CH_2), 2.35 (3H, s, ArMe), 2.25 (3H, s, COMe), 1.51 (3H, s, Me), 1.50 (3H, s, Me); *m/z* 231 (M, 20%), 174 (100), 128 (50), 127 (25); HRMS: M, found 231.1251. $C_{14}H_{17}NO_2$ requires 231.1260.

4.5.18. 1-Acetyl-3-chloro-2,2,6-trimethyl-1,2-dihydroquinoline 23. Potassium *tert*-butoxide (0.17 g, 1.2 mmol) was added to a stirred solution of the dichloro compound, **4**, (0.22 g, 0.77 mmol) in tetrahydrofuran (10 mL) and the resultant mixture was stirred under nitrogen for 24 h. Water (10 mL) was added and the mixture extracted with dichloromethane (3×15 mL). The combined organic extracts were dried and the solvent removed. The residue was purified by flash chromatography; elution with ethyl acetate/light petroleum (1:4) yielded the vinyl chloride, **23**, (0.065 g, 74%) as a yellow oil; δ_H 7.35 (1H, br s, ArH), 6.80–7.00 (2H, m, ArH), 5.85 (1H, s, C=CH), 2.40 (3H, s, ArMe), 2.15 (3H, s, COMe), 1.60 (6H, s, Me); *m/z* 249/251 (M, 20%), 234/236 (55), 192/194 (100); HRMS: M, found 249.0911. $C_{14}H_{16}ClNO$ requires 249.0920.

4.5.19. 1-Acetyl-2,2,6-trimethyl-1,2,3,4-tetrahydroquinoline-3-one 24. A mixture of the vinyl chloride, **23**, (0.15 g, 0.60 mmol) and mercuric acetate (0.26 g, 0.83 mmol) in trifluoroacetic acid (15 mL) was stirred at room temperature under nitrogen for 24 h. The mixture was filtered and the solvent removed. Saturated sodium bicarbonate (15 mL) and saturated sodium chloride (15 mL) were cautiously added to the residue and the resulting mixture was extracted with dichloromethane (3×20 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed. The residue was purified by flash chromatography; elution with ethyl acetate/light petroleum (1:4) yielded a fraction which contained predominantly the ketone, **24**, (0.10 g, 70%) as a yellow oil; ν_{max} ($CDCl_3$) 1730 cm^{-1}; δ_H 6.67–7.32 (3H, m, ArH), 3.06 (2H, s, CH_2), 2.32 (3H, s, ArMe), 2.23 (3H, s, COMe), 2.18 (6H, s, Me); *m/z* 231 (M, 20%), 189 (15), 188 (29), 174 (100).

4.5.20. 1-Acetyl-3-chloro-2,2,6-trimethyl-1,2,3,4-tetrahydroquinoline-4-one 25. A solution of chromium trioxide in sulfuric acid (30%, 0.07 mL, 0.19 mmol) was added to a stirred solution of the chlorohydrin, **11**, (0.05 g, 0.19 mmol) in acetone (2 mL) and the mixture stirred under nitrogen for 24 h. The mixture was diluted with water (5 mL) and extracted with dichloromethane (2×10 mL). The combined organic extracts were dried and the solvent removed. The residue was purified by flash chromatography; elution with ethyl acetate/light petroleum (3:7) yielded the ketone, **25**, (0.036 g, 73%) as a pale yellow oil; ν_{max} ($CDCl_3$) 1740 cm^{-1}; δ_H 7.85 (1H, d, J=2.2 Hz, ArH), 7.30 (1H, dd, J=2.2, 8.0 Hz, ArH), 6.85 (1H, d, J=8.0 Hz, ArH), 4.10 (1H, s, CHCl), 2.35 (3H, s, ArMe), 2.30 (3H, s, COMe), 1.70 (3H, s, Me), 1.40 (3H, s, Me); *m/z* 265/267 (M, 20%), 223/225 (30), 208/210 (50), 138 (100); HRMS: M, found 265.0863. $C_{14}H_{16}ClNO_2$ requires 265.0870.

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