THE SYNTHESIS OF VIRANTMYCIN ANALOGUES

A Thesis

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by

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The Synthesis of Virantmycin Analogues

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Statement

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Natalie M. Williamson

March, 1996

Abstract

A general synthesis of analogues of the antiviral drug virantmycin (1) is described. The key reaction in the sequence is the cyclization of an N-(1,1-disubstitutedpropargyl)aniline system to the corresponding 2,2-disubstituted-1,2-dihydroquinoline system, using cuprous chloride in refluxing toluene. For 2,2-dimethyl substituted systems, the rate of cyclization was found to be mainly dependent on the electronic nature of the *para*-aromatic substituent. Electron donating substituents, such as a methoxy group, accelerate the reaction, while electron withdrawing substituents, such an ester group, cause a decrease in the rate of cyclization. When the cyclization conditions were applied to N-propargyl anilines with methoxymethyl and *n*-butyl side chains α- to the nitrogen atom, cyclization to the dihydroquinoline was followed by spontaneous loss of dimethyl ether to give the corresponding 2-*n*-butylquinoline systems. This aromatization could be avoided by trapping the NH group of the dihydroquinoline as a trifluoroacetamide. N-propargylaniline systems with both the larger side chains and electron withdrawing *para*-substituents could not be cyclized to the corresponding dihydroquinolines. Attempted preparation of an N-(1,1-di-*n*-butylpropargyl)aniline system was unsuccessful, presumably due to the steric hindrance of the bulky butyl groups.

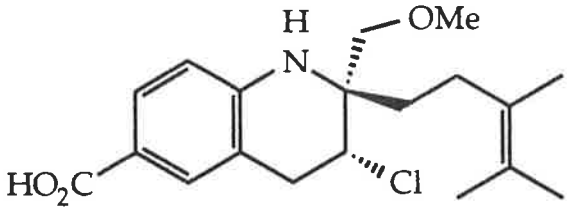
N-trifluoroacetyl protected dihydroquinolines were chlorinated to give 2,2-disubstituted-*cis*-3,4-dichlorotetrahydroquinolines. The mechanism of this reaction is discussed. Selective dechlorination of these dichloro compounds at the benzylic position provided the corresponding 3-chloro systems. The analogous 3,4-dibromo compound was also synthesized, but was found to be very unstable.

Other reactions of the N-acyldihydroquinoline system were investigated. *Trans*-chlorohydrins were formed from N-acyldihydroquinolines. The stereochemistry and mechanism of this transformation is discussed. Epoxidation of the dihydroquinoline double bond provided a 3,4-epoxy system, which was hydrogenolyzed at the benzylic position to give a 3-hydroxytetrahydroquinoline. Subjection of this alcohol to Mitsunobu conditions did not result in the formation of the expected 3-chloro derivative, but rather the 3-trifluoroacetate, formed by intramolecular transfer of the trifluoroacetyl group from the nitrogen atom to the oxygen atom. This trifluoroacetate was converted to the corresponding 3-chloro system by S_N2 displacement of the trifluoroacetate moiety with chloride ion.

The copper-catalyzed cyclization reaction was extended to N-(1,1-dimethylpropargyl)-2-aminoanthracene and several N-(1,1-dimethyl-propargyl)aminoquinolines. Also cyclized using the same conditions were *meta*- and *ortho*-substituted N-(1,1-dimethylpropargyl)aniline systems. N-methyl-N-(1,1-dimethylpropargyl)aniline did not cyclize to the corresponding dihydroquinoline, supporting the proposed mechanism for the cyclization. An N-propargyl aniline system possessing a hydrogen atom α- to the nitrogen atom cyclized to give the corresponding quinoline.

Introduction

Virantmycin[1-7] (1), a novel chlorine-containing amino acid isolated from the fermentation broth of *Streptomyces nitrosporeous*, is a potent antiviral drug which is active[1] against some RNA and DNA viruses. Virantmycin has also shown[2] *in vitro* activity against *Herpes simplex* types 1 and 2, as well as exhibiting weak antifungal activity.[3]

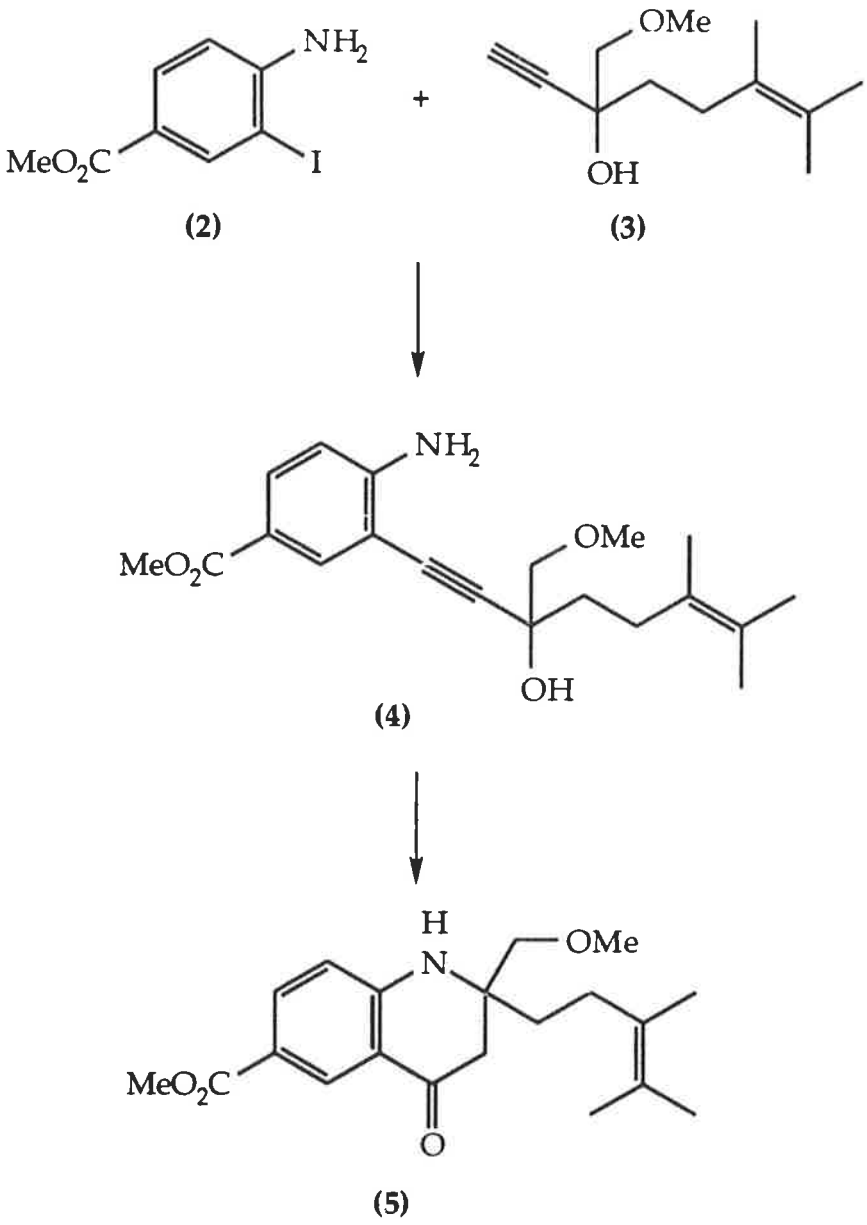


(1)

Because of possible applications of virantmycin in medicine, considerable effort has been devoted to the total synthesis of this compound. To date, there have been three reported syntheses of virantmycin.[2,4,5-7]

Hill and Raphael[2,4] synthesized (±)-virantmycin beginning with a palladium catalyzed coupling of the ester (2) with the acetylenic alcohol (3) (Scheme 1). Cyclization of the resulting alkynyl benzene (4) using methanesulphonic acid gave the tetrahydroquinolone (5) (Scheme 1).

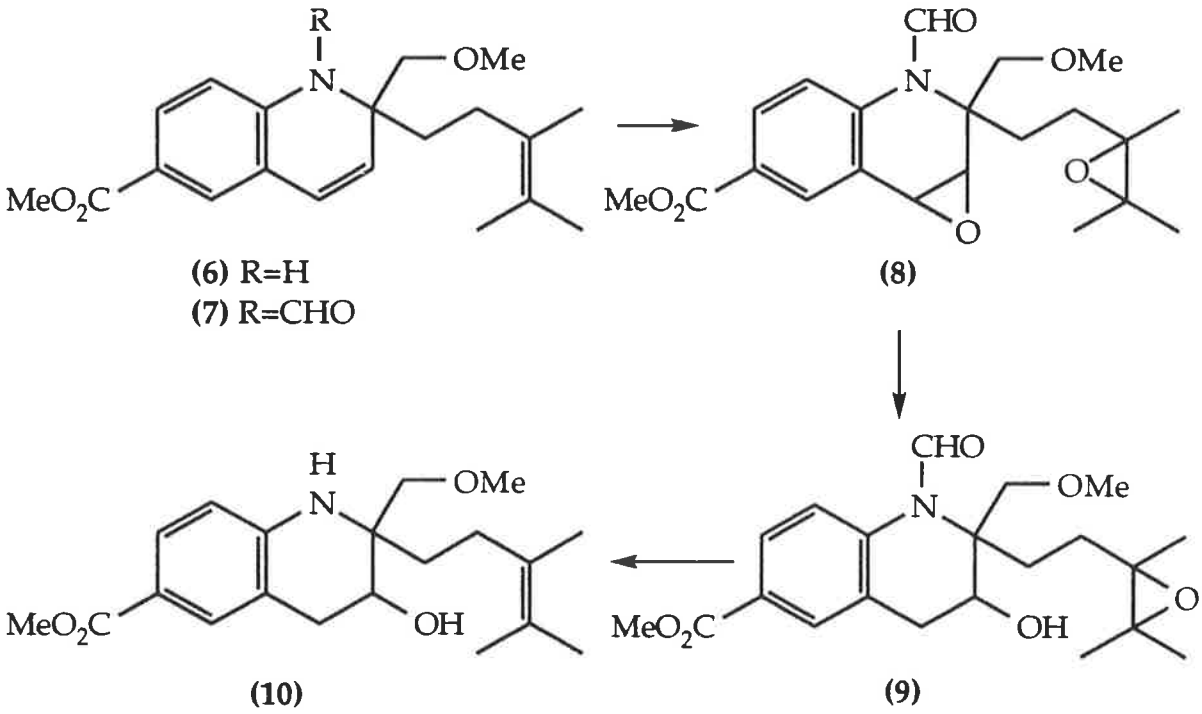
Reduction of (5) with sodium borohydride, followed by dehydration gave the dihydroquinoline (6), which readily lost dimethyl ether when heated to give the corresponding quinoline. Therefore, the synthesis was continued using the more stable N-formyl derivative (7).



Scheme 1

A diastereomeric mixture of *bis*-epoxides (8) was formed by treating (7) with an excess of *meta*-chloroperbenzoic acid. This mixture was selectively hydrogenolyzed to the hydroxyepoxide (9), reduced with tungsten hexachloride/butyllithium and deformylated to give a single diastereomer of the aminoester (10) (Scheme 2). S_N2 displacement of the hydroxy group of

(10) by chloride followed by ester hydrolysis gave an amino acid whose spectral and chromatographic properties were identical to those of natural virantmycin.



(6) R=H
(7) R=CHO

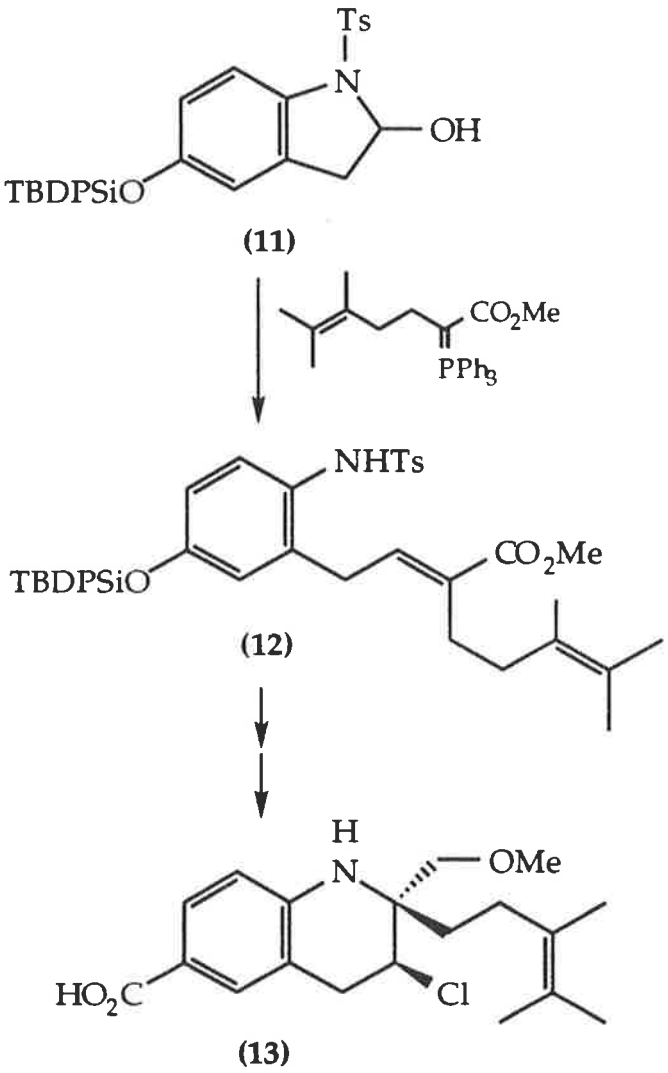
(8)

(10)

(9)

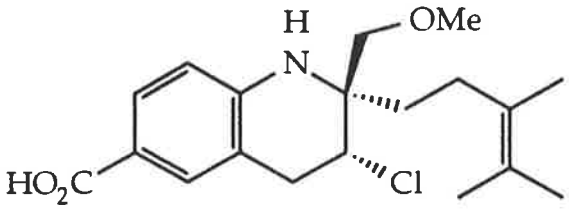
Scheme 2

A Japanese group[5-7] synthesized the basic virantmycin skeleton *via* two different routes. The first sequence,[5] which yielded antipodal virantmycin (13), began with a ring opening of the sulphonamide (11) to give (12) (Scheme 3). Subsequent modification of the side chain of (12), followed by cyclization using 2 equivalents of trifluoroacetic acid in toluene, gave the carbon framework of virantmycin.



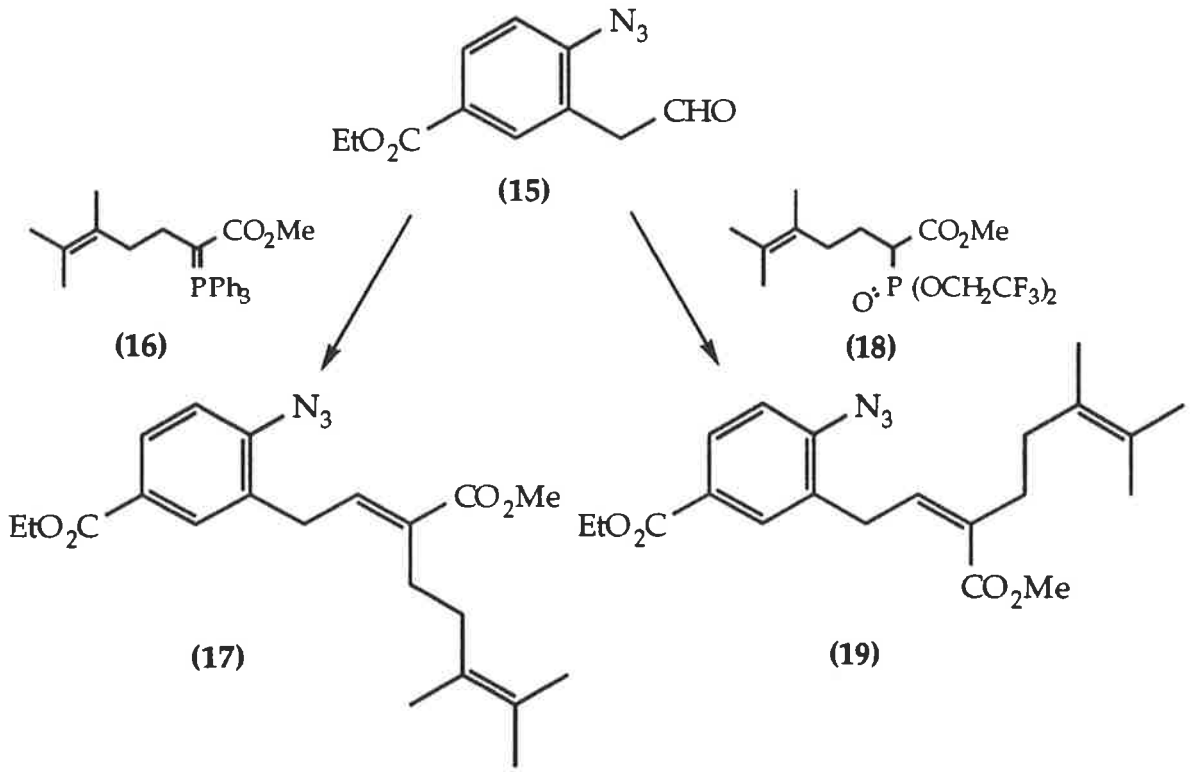
Scheme 3

The second route[6,7] was a stereospecific total synthesis of (±)-virantmycin and its diastereomer (±)-(14).



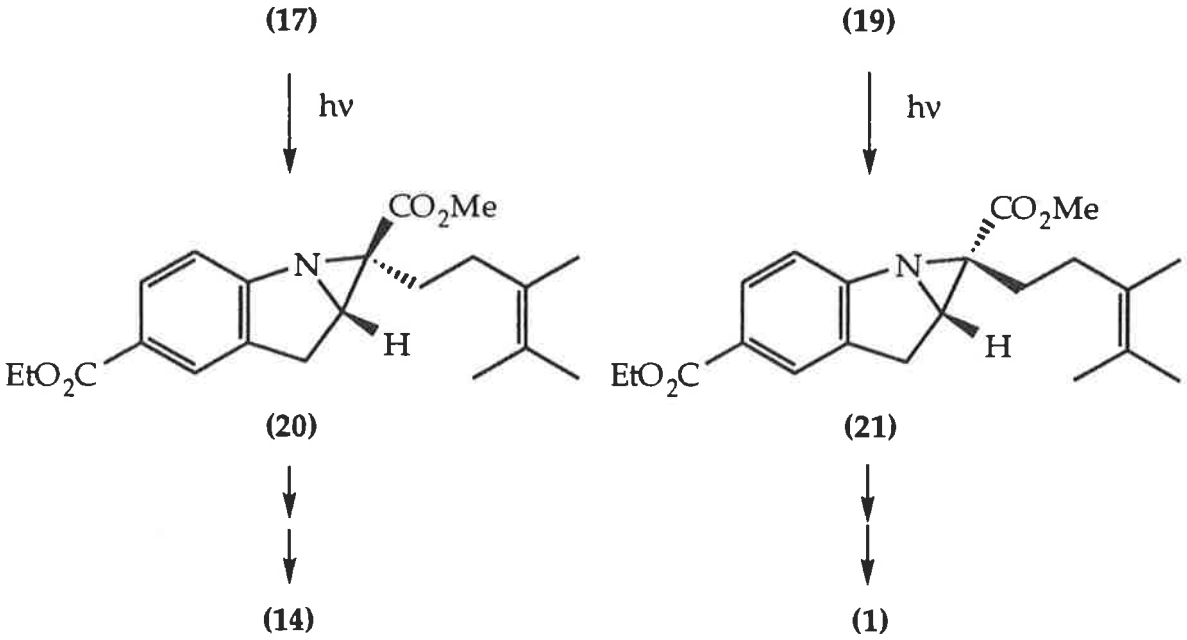
(14)

The sequence began with a Wittig reaction between the aldehyde (15) and the phosphorane (16) to yield the *E*-olefin (17). An alternative route, involving a Horner-Emmons reaction with (15) and the phosphonate (18) provided the *Z*-olefin (19) (Scheme 4).



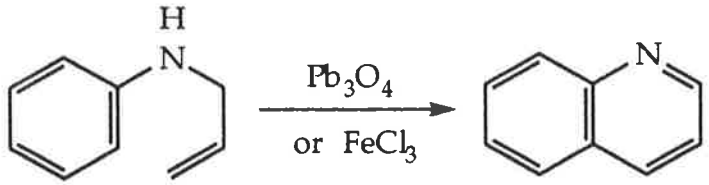
Scheme 4

Intramolecular nitrene addition induced by photolysis of both (17) and (19) yielded the aziridines (20) and (21) respectively (Scheme 5). Reduction of the ester group on the aziridine ring of (20) and (21), followed by methylation and highly selective ring opening gave (±)-(14) and (±)-(1) respectively (Scheme 5).



Scheme 5

There has been much work[31,32] carried out on the preparation of quinolines and dihydroquinolines from aniline systems, with the earliest synthesis of quinoline (23) reported by Koenigs[33] in 1879 (Scheme 6). Allyl aniline (22) was cyclized to the corresponding quinoline (23) using either lead oxide or ferrous chloride as a catalyst.

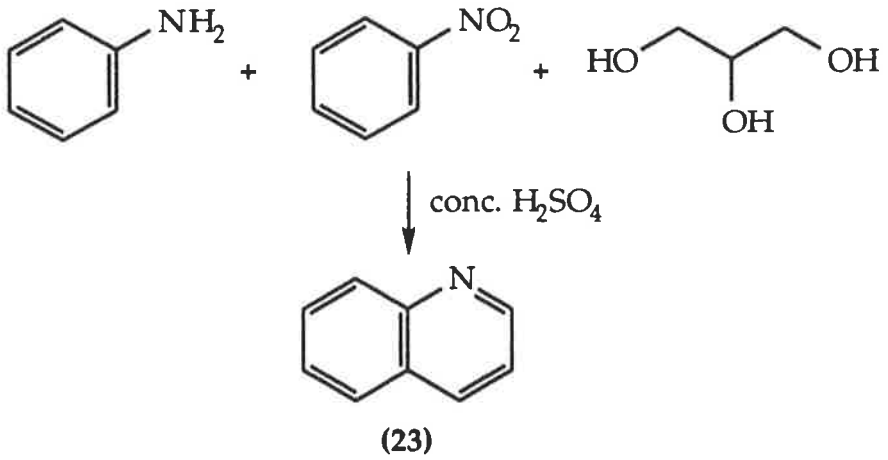


(22) (23)

Scheme 6

A common feature of many subsequent syntheses of quinoline systems from anilines with the above method[33] is formation of the C-N bond *via* N-alkylation followed by electrophilic ring closure.

In 1881, Skraup[34,35] reported the synthesis of quinoline (23) from aniline, glycerol, nitrobenzene and concentrated sulphuric acid (Scheme 7).



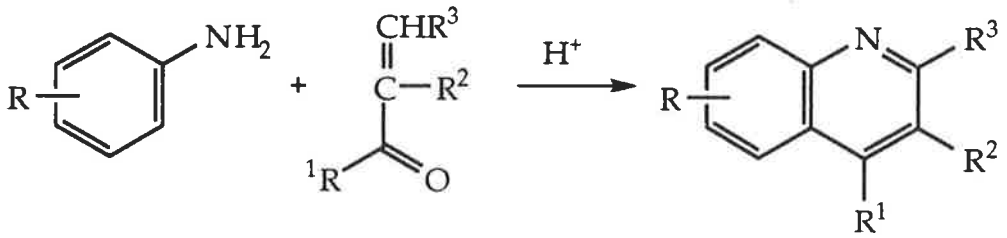
(23)

Scheme 7

Earlier investigations by Skraup[33,34] showed that yields of quinoline were poor unless nitrobenzene was used as part of the reaction mixture, and it was

later proposed[35] that the nitrobenzene was required to oxidize an intermediate dihydroquinoline species to the quinoline (23).

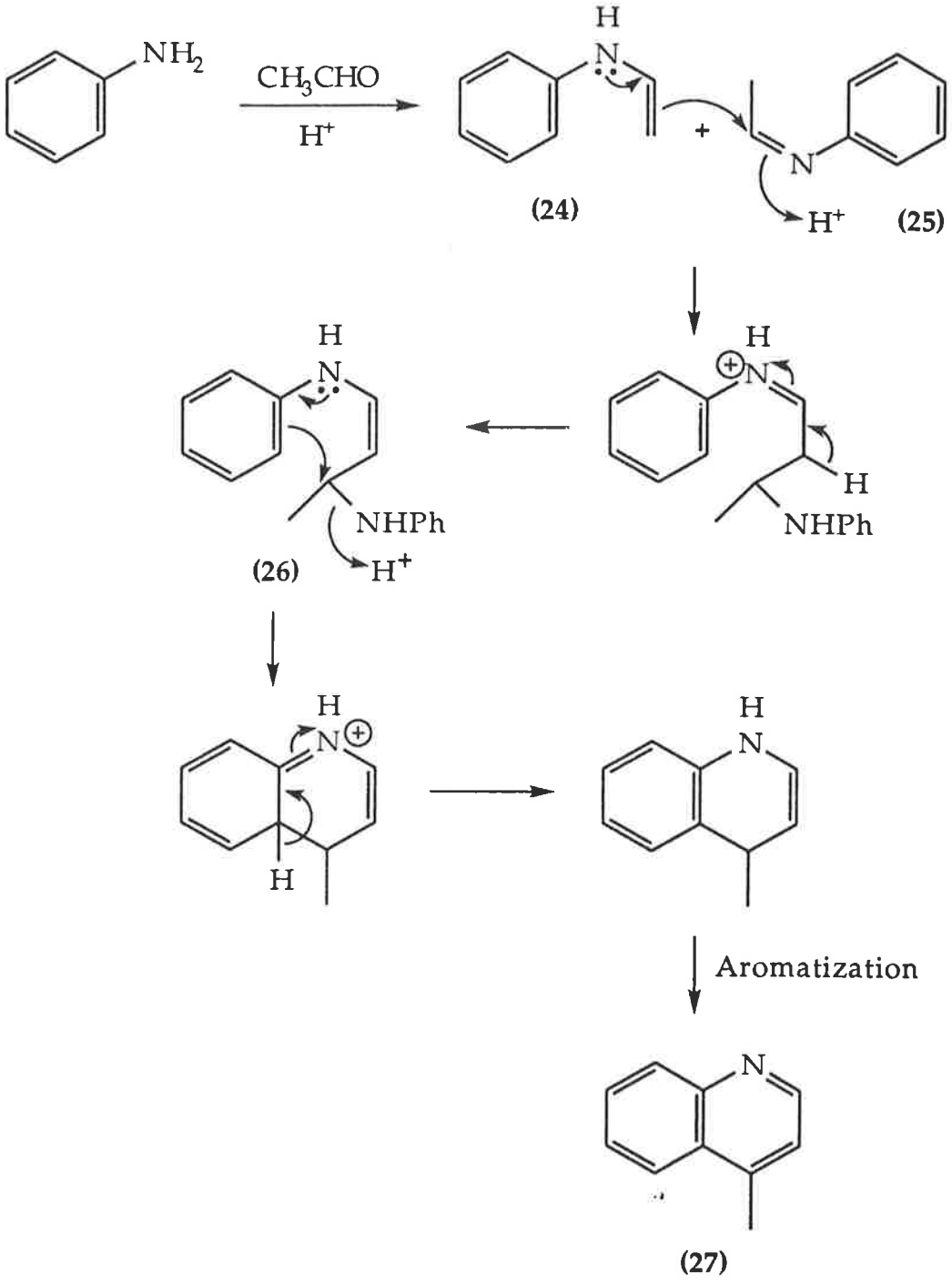
The more general Doebner-von Miller synthesis[37] of quinolines was also published in 1881, and involves the reaction of a substituted aniline with an α,β-unsaturated carbonyl system under acid catalysis (Scheme 8).



Scheme 8

The Doebner-von Miller synthesis provided a high yielding route to a large variety of substituted quinolines, since the reaction conditions were found[37] to tolerate a wide range of substituents (R, R^1, R^2, R^3) except acid-sensitive moieties. This led to the synthesis of a wide range of quinolines with halogen, alkyl and aryl substituents. It was found,[37] however, that if the substituent on the aniline component was electron withdrawing, yields of quinolines were poor; and that if a *meta* substituted aniline was used, a mixture of quinoline products was obtained.

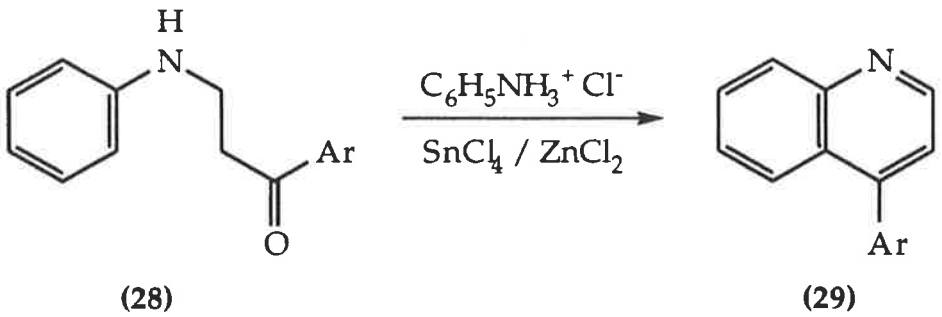
The reaction[38] of aniline with acetaldehyde to give the quinoline (27) (Scheme 9) is a variation of the Doebner-von Miller process.[37] The initial step of the reaction involves the condensation of aniline with acetaldehyde to give the enamine (24), which then reacts with the imine (25) (also formed under the reaction conditions) to give the intermediate (26). Cyclization of (26) followed by aromatization gives the quinoline (27) (Scheme 9).



Scheme 9

Another example of electrophilic ring closure onto a carbonyl carbon was reported by Dennis and Butskus,[39] who cyclized the N-alkyl aniline (28) to the

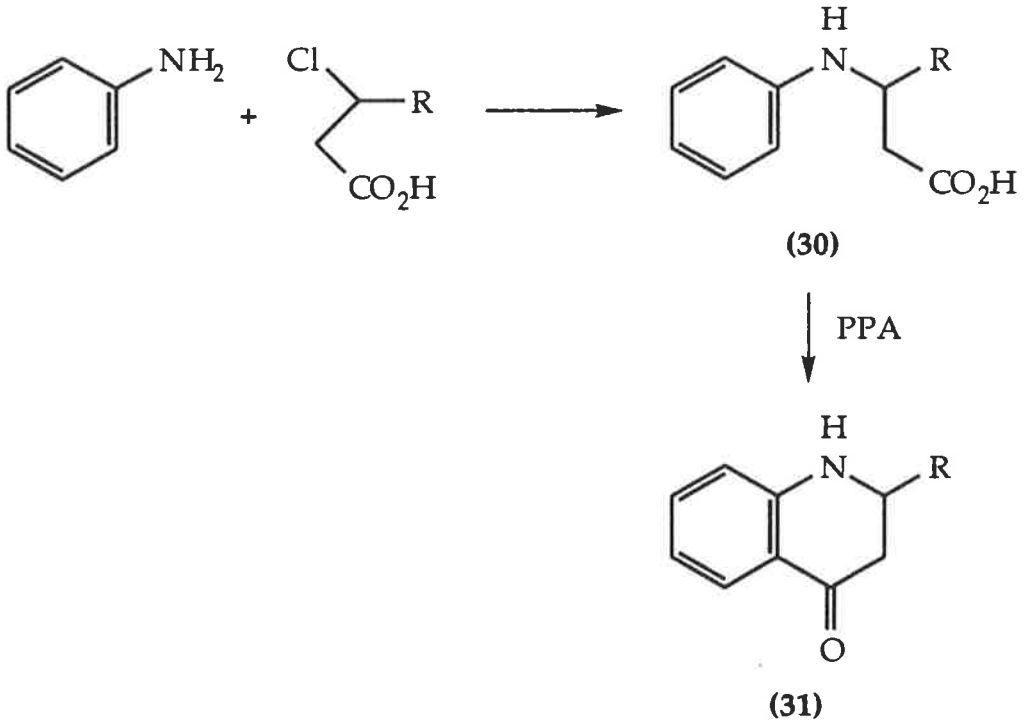
corresponding quinoline (29) using a tin chloride-zinc chloride catalyst (Scheme 10).



(28) **(29)**

Scheme 10

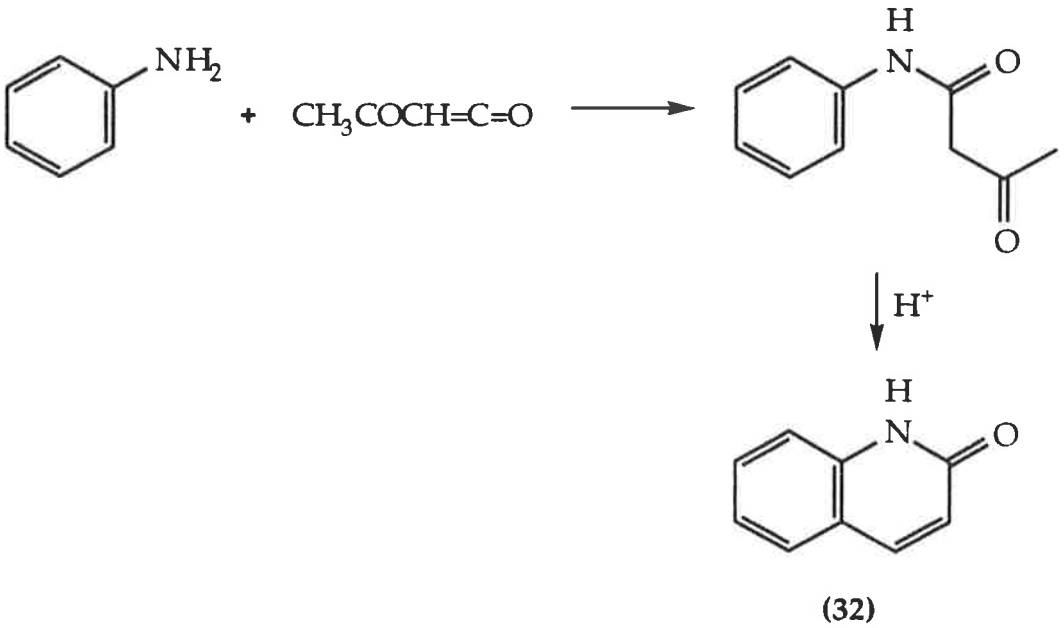
Koo[40] reacted aniline with substituted 3-chloropropionic acids to obtain N-alkylated systems such as (30), which were cyclized to the quinolone structure (31) using polyphosphoric acid (PPA) (Scheme 11).



(30) **(31)**

Scheme 11

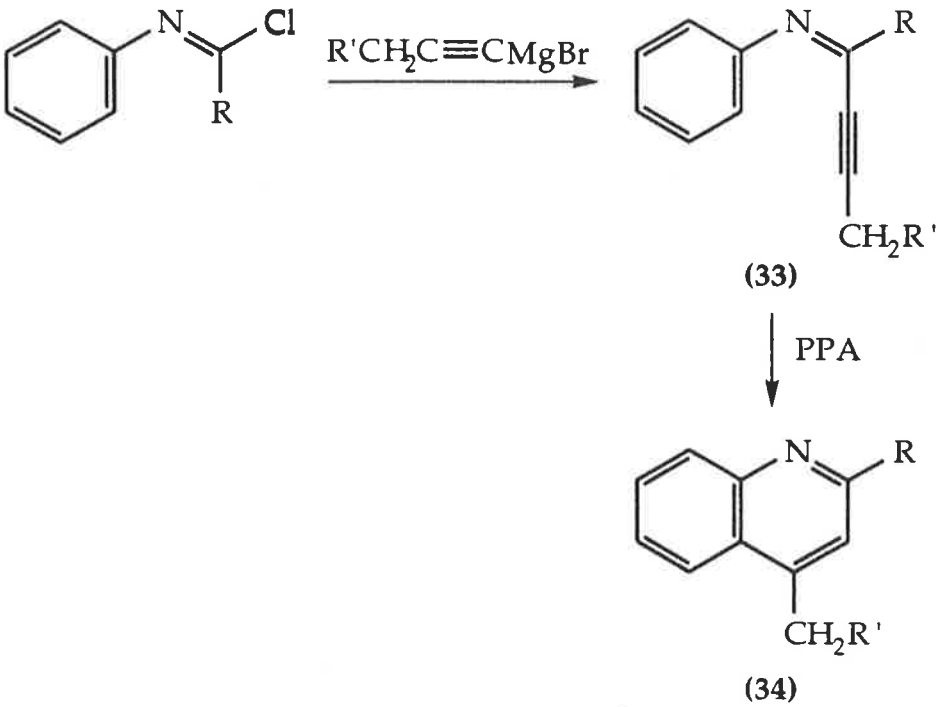
The Knorr synthesis[41] of 2-quinolones involves the initial reaction of an aniline with an acetylketene to give a diketo species which is cyclized to the quinolone (32) using acid catalysis (Scheme 12).



(32)

Scheme 12

Ried and Weidemann[42] synthesized substituted quinolines by cyclizing the alkyne system (33) under acidic conditions (Scheme 13). The cyclization of the enyne (33) is thought to proceed *via* an *exo* cyclization of an allene intermediate.[42]

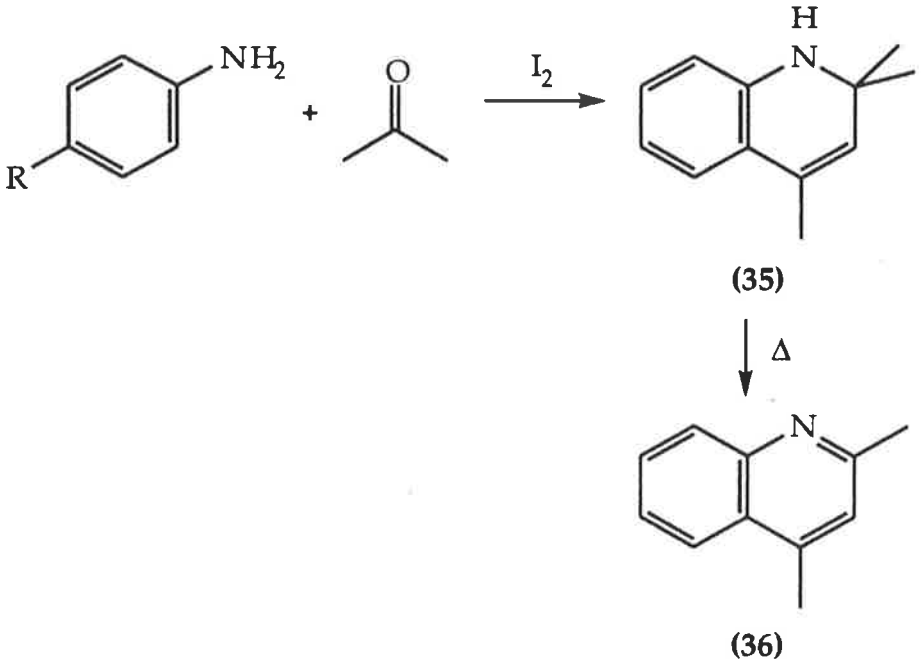


Scheme 13

Most of the quinoline syntheses reviewed here are not suitable for use in our planned synthesis of virantmycin (1), since the latter possesses the partially reduced tetrahydroquinoline structure. Even if these previously reported quinoline syntheses could be adapted for the synthesis of the more easily manipulated dihydroquinoline system, obtaining the required starting N-alkyl anilines would pose problems, since the α-disubstituted system could not be synthesized *via* conventional S_N2 attack on an alkyl halide.

Engler and Riehm[43] observed an unexpected product from the reaction of aniline systems with acetone and iodine; Knoevenagel and Jager[44] isolated the new product, but it was not fully characterized until Reddelien and Therm[45] correctly identified it as the dihydroquinoline (35) (Scheme 14). Loss

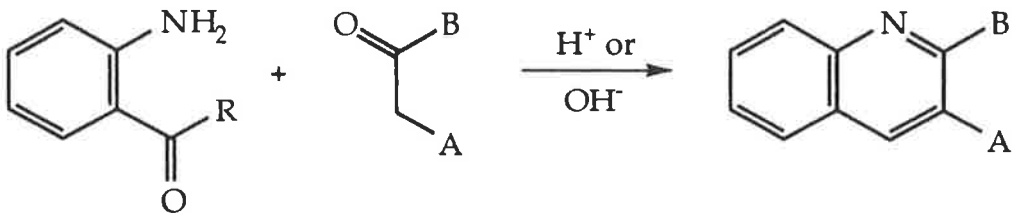
of methane to give the fully aromatic quinoline (36) was achieved[43,52] by heating the dihydroquinoline (35) (Scheme 14).



Scheme 14

The latter dihydroquinoline preparation has only been reported using acetone as the ketone, and is not entirely suitable for use in our planned synthesis because the product dihydroquinoline possesses an unwanted alkyl substituent at the 4-position.

Quinolines have also been prepared by the Friedländer synthesis[46], which involves the condensation of *ortho*-carbonyl substituted anilines with another carbonyl compound (Scheme 15, R=H).

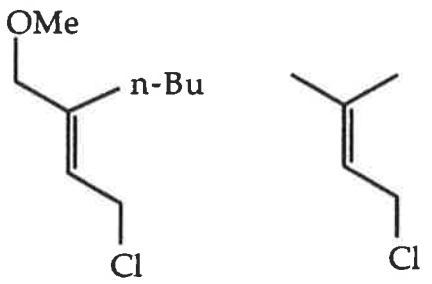


Scheme 15

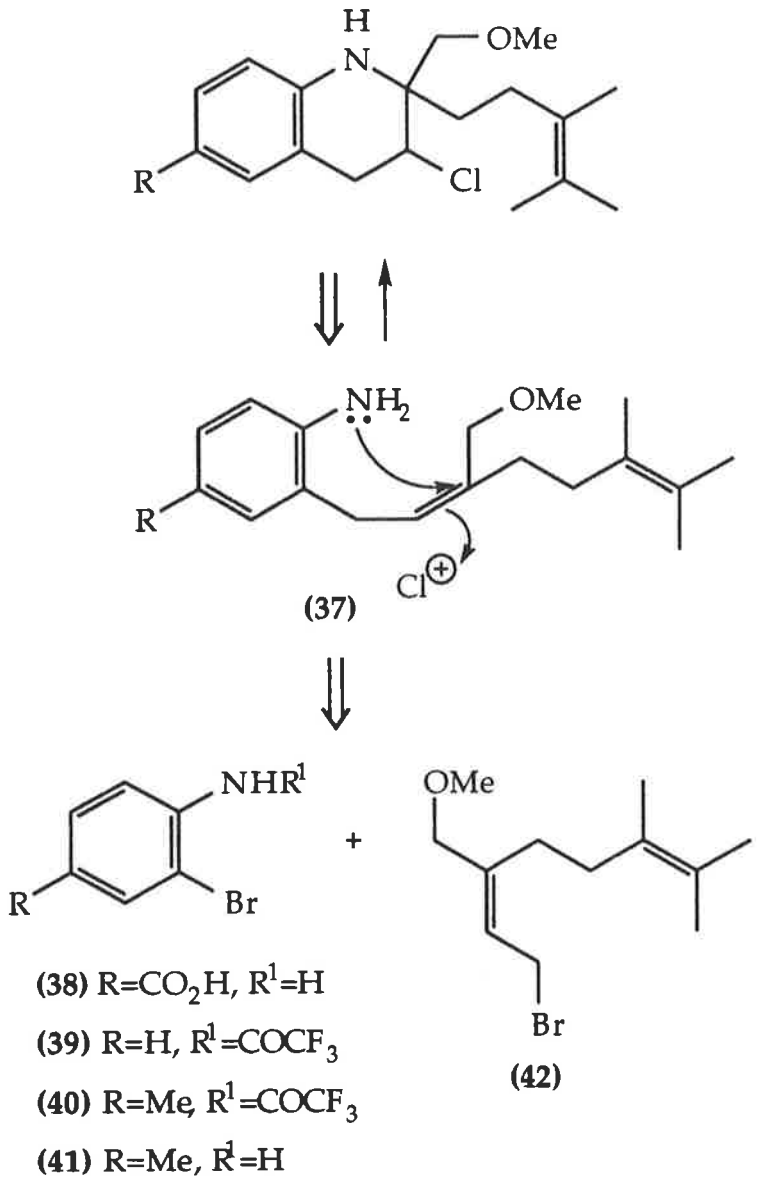
Other similar syntheses to the Friedländer process include the Camps modification,[47] the von Niementovski modification[48] and the Pfitzinger modification.[49-51]

Initial approaches by our group to the synthesis of virantmycin and/or virantmycin analogues were investigated by Raner[8] and Francis,[9,27] following the retrosynthetic analysis outlined in Scheme 16.

Allyl benzenes related to (37) were synthesized using the subunits (39) and (44) *via* a lithium-halogen exchange of the aromatic bromine atom of (39) followed by the addition of (44).[8] Compound (43) was also used as a model[9,27] in order to conserve stocks of (42), which was synthesized *via* a lengthy series of reactions.[9,27]

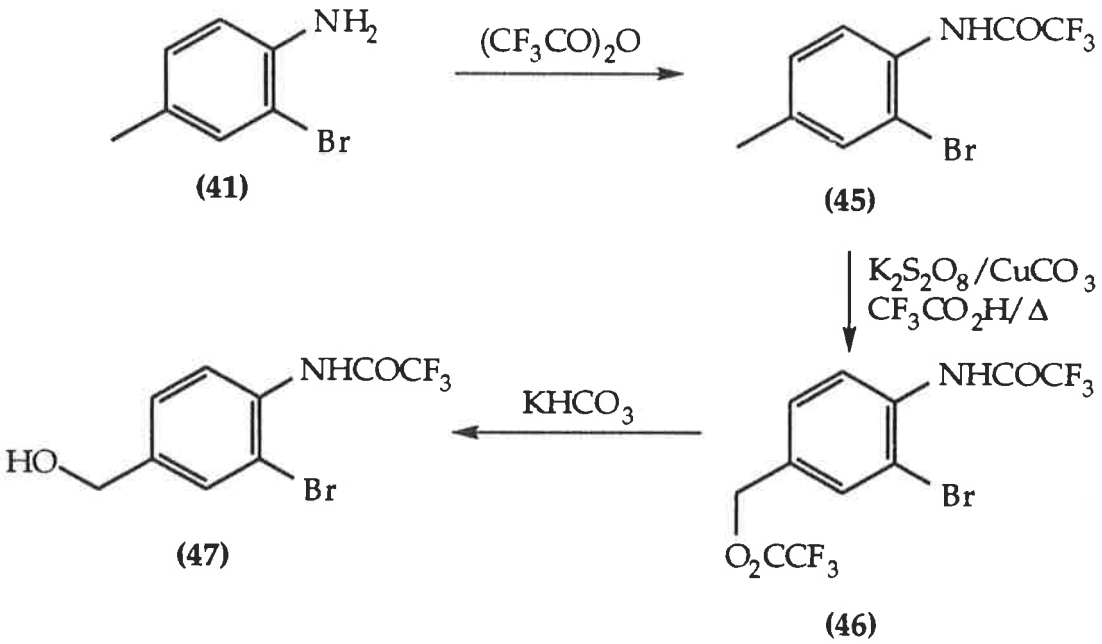


(43) **(44)**



Scheme 16

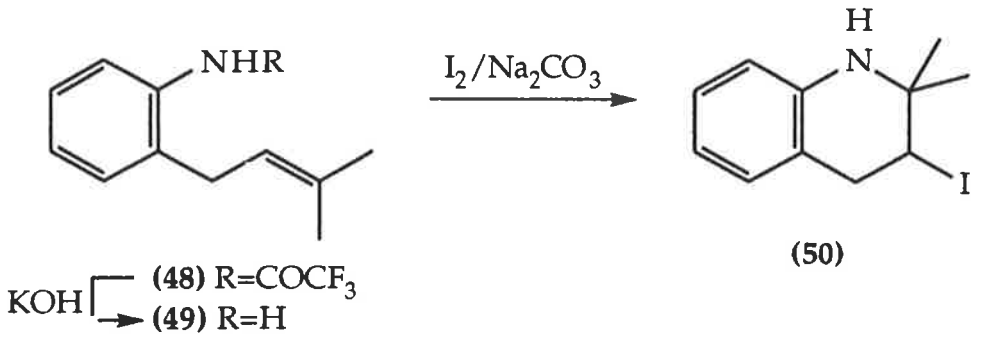
Raner[8] established a preparation of an appropriate aromatic subunit where the carboxylic acid function is masked as a benzylic alcohol (Scheme 17).



Scheme 17

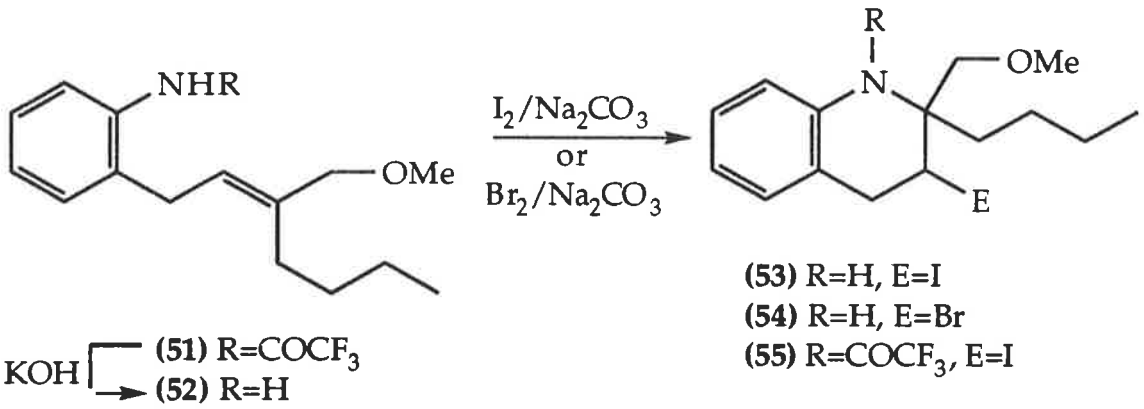
Protection of commercially available 2-bromo-4-toluidine (41) gave the trifluoroacetamide (45), followed by oxidation at the benzylic position to give the trifluoroacetate (46). Hydrolysis of the ester using potassium bicarbonate in aqueous methanol yielded the benzylic alcohol (47).

The allylbenzenes (51) and (48), formed from the reaction of (39) with (43) and (44) respectively, were obtained in good yields[8,27] and subsequent deprotection to give the free amines (52) and (49) was easily achieved using methanolic potassium hydroxide. Raner[8] showed that iodine-induced electrophilic cyclization of (49) was a viable method for the production of the 2,2-dimethylsubstituted tetrahydroquinoline (50) (Scheme 18).



Scheme 18

Francis[9,27] further investigated this electrophile-induced cyclization with more complicated systems such as (52) (Scheme 19).

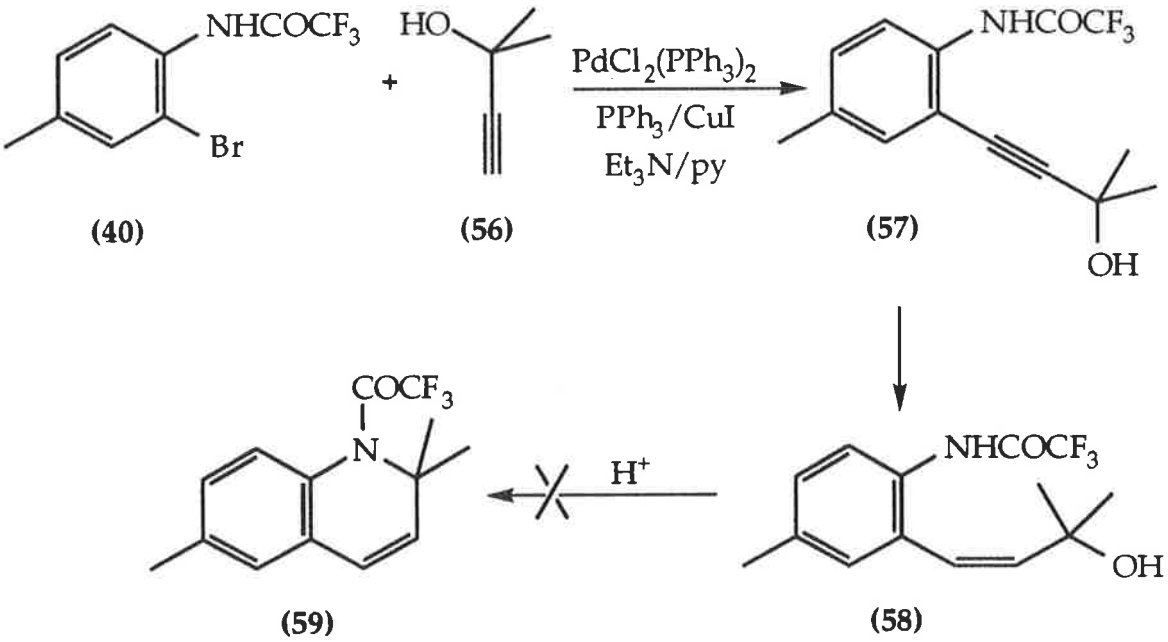


Scheme 19

The reported cyclization procedure,[8] using one equivalent of iodine and sodium carbonate in dichloromethane for 4h resulted in an intractable mixture when applied to (52).[27] Other attempts at cyclizing (52), using either modifications of the original reaction conditions and/or the use of bromine as

an electrophile were unsuccessful.[27] A trace amount of the iodotetrahydroquinoline was trapped as the trifluoroacetamide (55), but the low yield meant that the step was not synthetically viable.[27] Therefore, it was concluded[27] that electrophile-induced cyclization of allylanilines was not a suitable approach in the synthesis of tetrahydroquinolines with the larger methoxymethyl and *n*-butyl side chains.

Francis[9] also investigated another approach to the virantmycin system, outlined in Scheme 20. The subunit (40) was coupled to the acetylene (56), using previously reported chemistry,[2,4] and Lindlar hydrogenation[53] of the triple bond of (57) gave the *cis*-alkene (58).



(40) **(56)** **(57)** **(59)** **(58)**

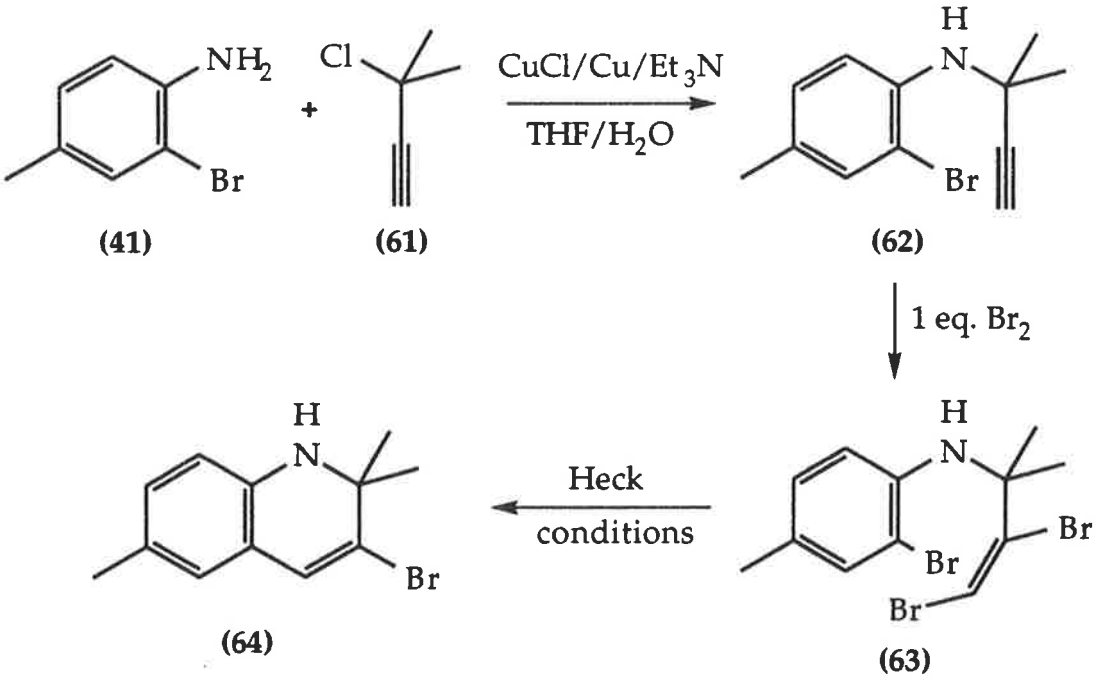
Scheme 20

The alkynylbenzene (57) and the *cis*-alkene (58) were both prepared in good yields;[9] however, attempts to cyclize (58) under acidic conditions resulted in

the recovery[9] of a complex mixture of products containing the diene (60), formed from the dehydration of (58).

(60)

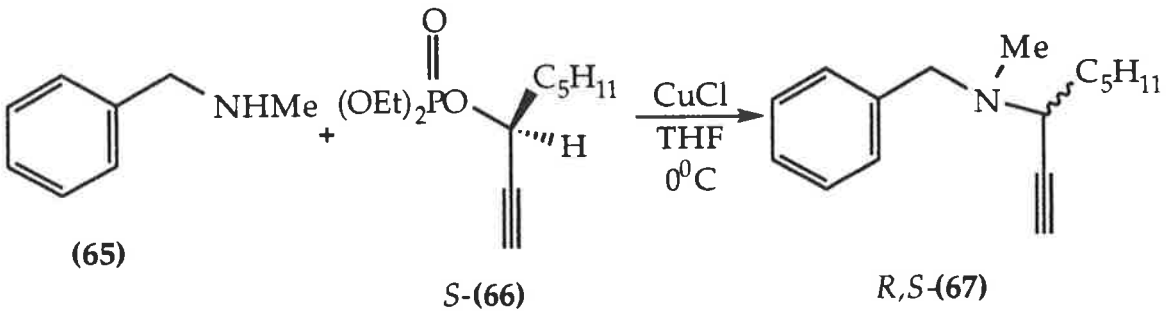
A different approach[9,10] to the synthesis of a precursor to the required tetrahydroquinoline system was investigated by Francis[9] and March[10] (Scheme 21). This method also involved palladium chemistry, but the order of formation of the two key bonds was reversed. They used a literature



(41) **(61)** **(62)** **(63)** **(64)**

Scheme 21

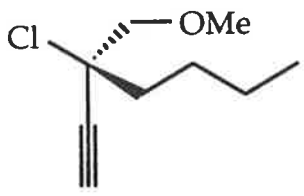
procedure involving the copper catalyzed coupling[10-13] of *tert*-chloroacetylenes such as (61) to aniline systems, which has been reported to give the resulting N-propargyl anilines in good yields. Although the exact mechanism of this coupling reaction is not known, it is thought to proceed *via* an S_N1-type process through a dipolar-type intermediate[30] (see page 44). Supporting this proposal is the fact that the product (67) of the reaction[20] between *S*-(66) and N-methylbenzylamine (65) was not optically active (Scheme 22).



(65) *S*-**(66)** *R,S*-**(67)**

Scheme 22

A problem with this approach to the synthesis of N-propargyl anilines is that this type of coupling reaction allows no stereochemical control at the carbon centre α- to the nitrogen atom. Thus, it would follow that any products from the reaction of an aniline with a chiral chloroalkyne such as (68) will be racemic.

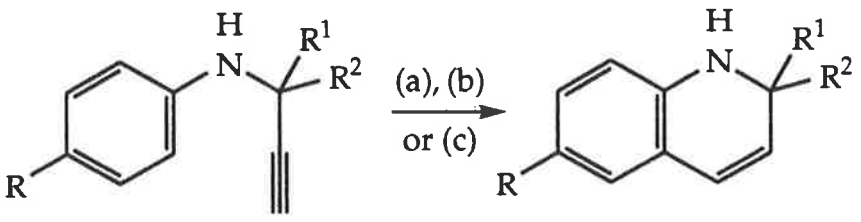


(68)

Although any virantmycin analogues resulting from a sequence that incorporated a coupling reaction (such as the one shown in Scheme 21) would, for the above reasons, be racemic at the carbon centre adjacent to the nitrogen atom, this avenue of research was pursued, since it would still be of interest to determine the biological activity of these racemic analogues.

Reaction of (41) with the chloroalkyne (61) yielded the N-propargyl aniline (62) in good yield.[9,10] Controlled bromination of the alkyne (62) gave the *E*-dibromoalkene (63);[9,10] however, attempts to cyclize the latter under a variety of conditions were unsuccessful.[9,10]

It has been reported in the literature[10-12,21] that acetylenic systems such as (69) can be cyclized to the dihydroquinoline. Jolidon and Hansen[11] achieved cyclization using copper catalysis and triethylamine in a refluxing tetrahydrofuran/water mixture (Scheme 23, conditions (a)), while Easton and Hennion[12,21] reported that cyclization occurs when systems such as (69) are treated with aniline hydrochloride, cuprous chloride and copper bronze while stirring at room temperature in an ethanol/water mixture (Scheme 23, conditions (b)).



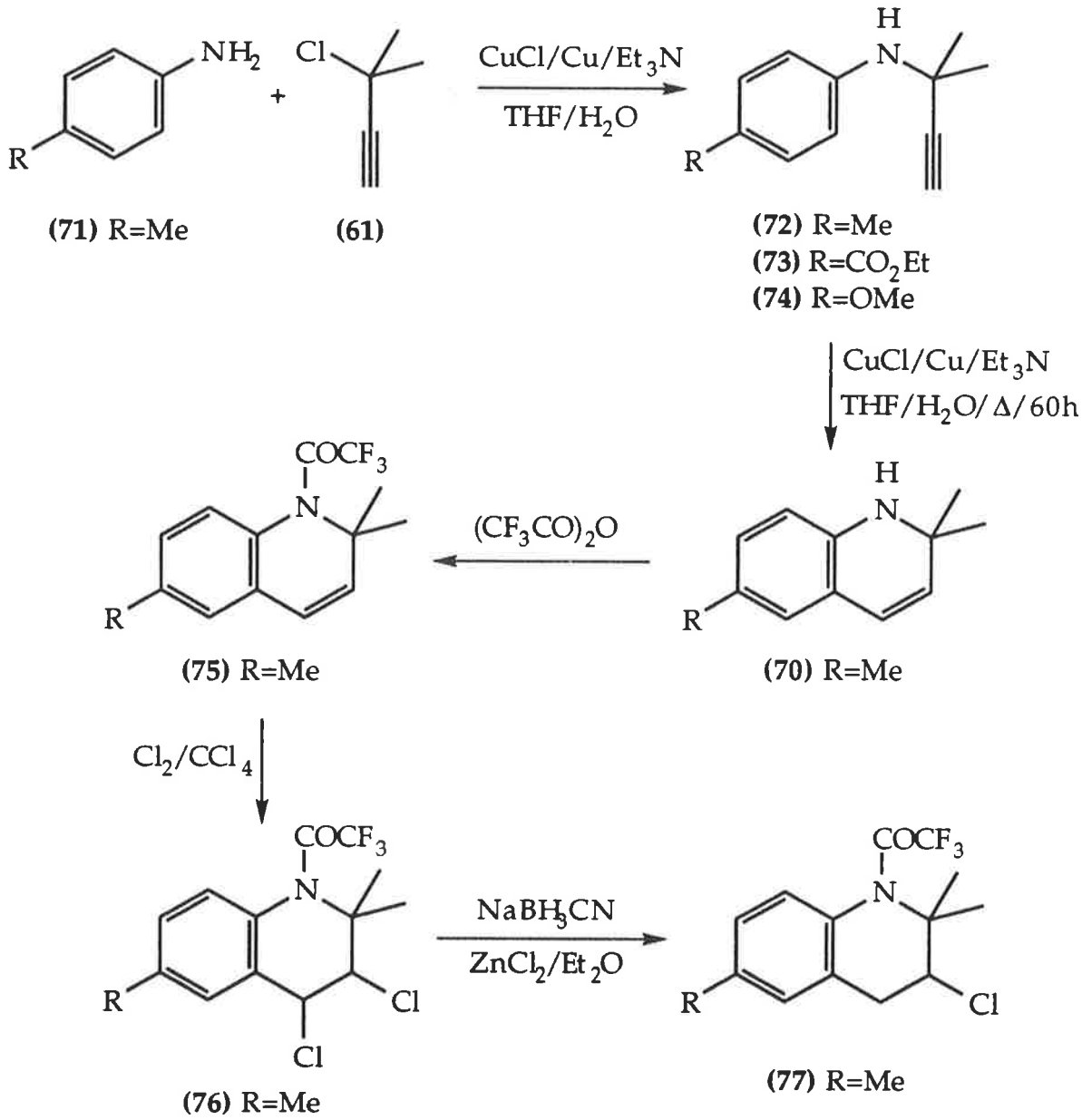
(69) **(70)** R=R¹=R²=Me

(a) $CuCl/Cu/Et_3N/THF/H_2O/\Delta$
(b) $PhNH_3Cl/CuCl/Cu/H_2O/EtOH$
(c) CuCl/toluene/Δ

Scheme 23

These two reaction conditions differ in that one is a thermal process occurring under basic conditions while the other takes place under acidic conditions at room temperature. However, both require copper catalysis.

March,[10] in a preliminary investigation, studied the cyclization method of Jolidon and Hansen[11] as an approach to the chloro compound (77) (Scheme 24); which, after deprotection would yield a molecule structurally similar to virantmycin. The chloroalkyne (61) was coupled to *p*-toluidine (71) using the copper chemistry described previously.[10-13] Cyclization of (72) to the dihydroquinoline (70), followed by N-trifluoroacetylation provided (75) in good yield. Treatment of (75) with a solution of chlorine in carbon tetrachloride afforded a near-quantitative yield of the dichloro compound (76).[10] The benzylic chlorine atom was selectively removed using the zinc-modified cyanoborohydride chemistry reported by Kim *et al*[22] to give the 3-chloro compound (77).[10] However, problems were encountered during this last step, where incomplete reaction was observed, causing difficulties in the purification of the desired product (77).[10] Throughout the sequence, none of the compounds were completely purified or characterized.



(71) R=Me **(61)**

(72) R=Me
(73) R=CO_2Et
(74) R=OMe

(75) R=Me **(70)** R=Me

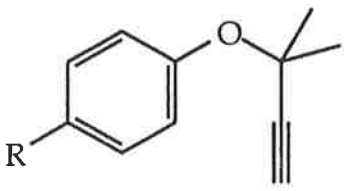
(76) R=Me **(77)** R=Me

Scheme 24

More recently, work[14] in our group has revealed that the cyclization of N-propargyl anilines also proceeds using cuprous chloride in refluxing toluene (Scheme 23, conditions (c)). This new method of cyclization was developed when earlier studies[14] indicated that the reported cyclization procedures[10,11,12,21] were extremely unreliable. Distillation of the crude N-

propargyl aniline (72) resulted in the recovery of a significant amount of the dihydroquinoline (70) as well as purified (72). This work suggested that previously reported cyclizations may have occured during the purification of the crude dihydroquinoline, due to traces of copper that may still have been present. This result prompted the investigation of the cyclization reaction as a thermal, copper dependent process, and led to the development of the cuprous chloride/refluxing toluene procedure.[14] The cuprous chloride/refluxing toluene method was found to be useful for the preparation of a wide range of dihydroquinolines as well as being the most reliable method of cyclization, and so was adopted for use in all further syntheses.

A brief mechanistic study[14] of the cyclization reaction using the cuprous chloride/refluxing toluene conditions was undertaken by gauging the effect of different *para*-substituents on the aromatic ring on the time taken for complete cyclization. Cyclization of the N-propargyl aniline (73) proceeded at a much slower rate than that of the reference compound (72); with the former requiring 16 hours at reflux for total conversion to the corresponding dihydroquinoline, compared to a reaction time of 1 hour for (72).[14] The alkyne (74) required only a 20 minute reaction time[14] for complete cyclization. Iwai and Ide[23] have reported that for the oxygen analogue (78), an electron donating R group enhanced the rate of cyclization and an electron withdrawing R group resulted in reduced yields.

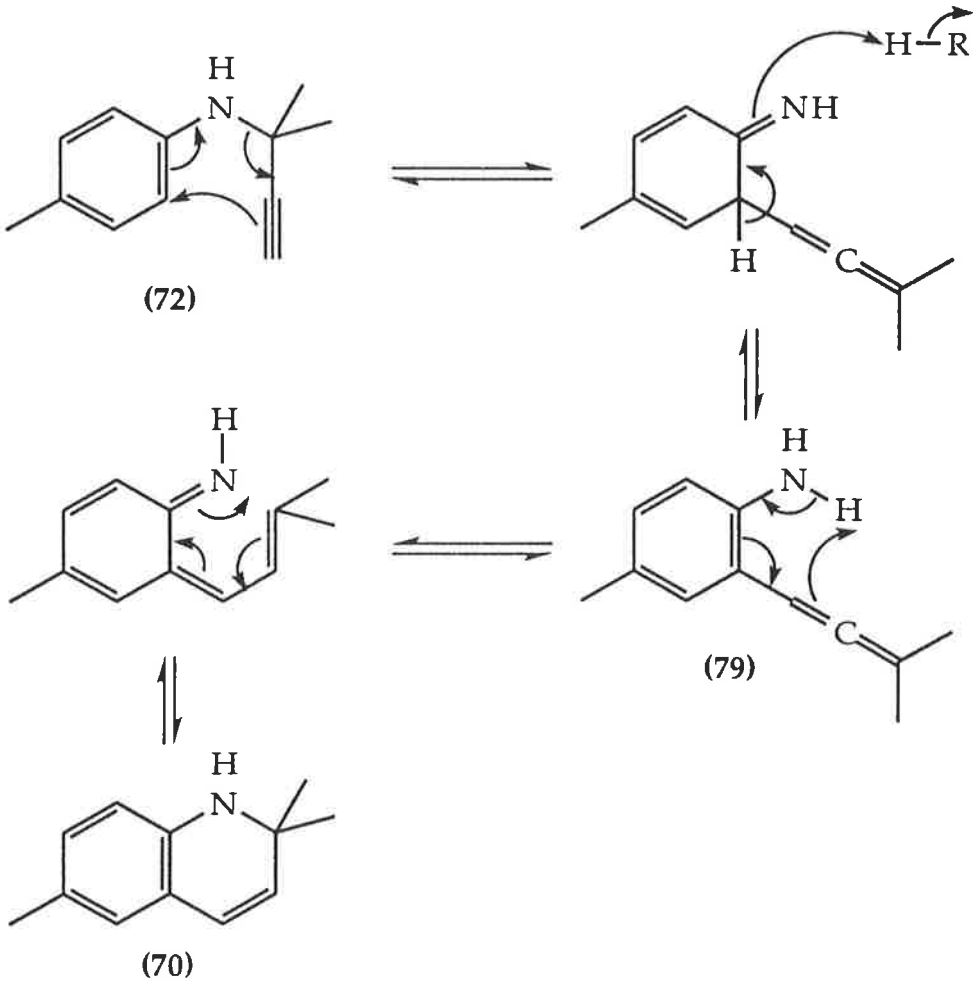


(78)

Assuming that the latter observation refers to the fact that electron withdrawing groups slow the cyclization rate, it was recognized[14] that the same observations apply to the N-propargyl aniline system (69). Iwai and Ide[23] proposed that the cyclization of (78) involved electrophilic attack by the triple bond on the aromatic ring. The above results for the nitrogen-containing system led to the conclusion[14] that the latter was likely to follow a similar mechanism.

A possible mechanism[19] for the cyclization of the N-propargyl aniline system is depicted in Scheme 25; and proceeds *via* a series of electrocyclic rearrangements and hydrogen shifts. The role played by copper is not yet clear, although it may stabilize the allene intermediate (79) in some way.

This new cyclization method was used instead of the cyclization conditions shown in Scheme 24 and the yields for the other reactions shown in that scheme were optimized.[14] The problem of incomplete reaction[10] encountered in the selective dechlorination was overcome by extending the recommended reaction time. Purification by flash chromatography provided[14] the pure, crystalline chloro compound (77) in an overall yield of 19% for the reaction sequence.



Scheme 25

Therefore, with a view to expanding and elaborating work previously carried out in this area, the aims of this project were:

1. to investigate the applicability of the copper catalyzed cyclization reaction in the synthesis of virantmycin analogues,

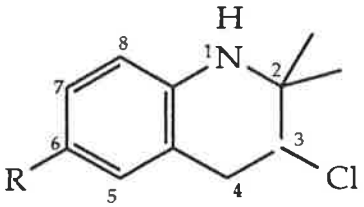
2. to synthesize a number of virantmycin analogues with a variety of alkyl groups adjacent to the nitrogen atom and on the aromatic ring,

3. to conduct a study of the effect of the aromatic R group on the copper-catalyzed coupling and cyclization reactions, and

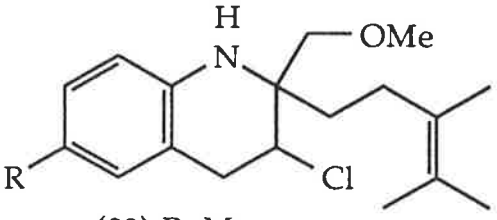
4. to study the suitability of the coupling reaction for use with larger aromatic systems such as aminoquinolines.

Aim 1

The major aim of this project was to develop the cyclization procedure shown in Scheme 23 (conditions (c)) and investigate its suitability for a general synthesis of virantmycin analogues such as (80)-(85). These analogues would then be tested for their antiviral and/or antifungal activity.



(80) R=Br
(81) R=NHAc
(82) R=OH



(83) R=Me
(84) R=OMe
(85) R=CO_2Et

Although it was planned that the side chains α- to the nitrogen atom would be varied, the 2,2-dimethyl-substituted analogues (80)-(82) were initial targets due to their relative simplicity. More complicated targets such as (83)-(85) would then be constructed using the chemistry developed to synthesize the 2,2-dimethyl-substituted analogues.

Aim 2

It was anticipated that the R group on the aromatic ring could also be varied, provided that its functionality was compatible with the chemistry used to construct the desired carbon skeleton. The eventual aim of the synthesis would be to incorporate a wide range of R groups onto the aromatic ring - such as halogen, hydroxy and amido groups - with particular focus on groups that could be elaborated to an ester or a carboxylic acid, providing an analogue extremely similar in structure to virantmycin (1). Initial studies[8-10,14,27] of the synthesis of virantmycin analogues by our group used unsubstituted or methyl-substituted aromatic precursors in order to establish appropriate reaction conditions. This study aimed to broaden the range of R groups on the aromatic ring.

Another possible site for variation is at C3, where the chlorine atom could be replaced with a different halogen (such as bromine) to give a different series of analogues.

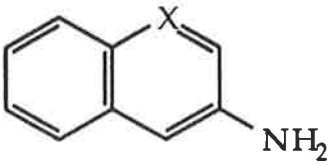
It was also of interest to investigate other reactions of the dihydroquinoline system, such as its reactivity towards epoxidation and chlorohydrin formation.

Aim 3

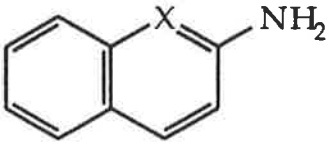
Studies of the copper-catalyzed coupling and cyclization reactions using a range of electron withdrawing and donating groups on the aromatic ring would be of use in clarifying mechanistic aspects of these reactions, particularly the cyclization, since its mechanism has yet to be fully elaborated.

Aim 4

Also of interest was the study of the coupling reaction between the chloroalkyne (61) and extended aromatic systems such as (86)-(89). An aminoquinoline series (using compounds such as (88) and (89)) would be an interesting subject for an initial study, since it could be determined what effect (if any) the nitrogen atom in the heterocyclic ring had on the reactivity of the amino group towards the coupling reaction.

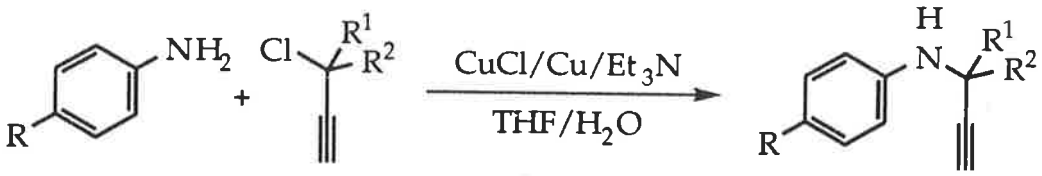


(86) X=CH
(88) X=N



(87) X=CH
(89) X=N

Chapter 1 - The Coupling Reaction



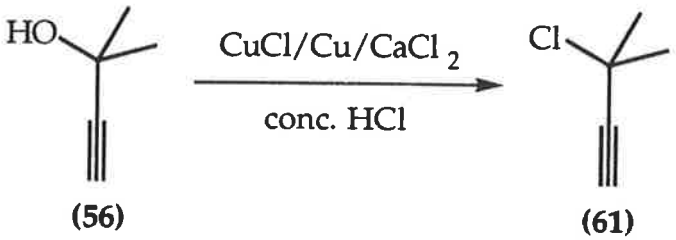
The aim of this chapter was to determine the scope of the coupling reaction by studying its tolerance of a wide range of R, R^1 and R^2.

It was of interest to see whether the chemistry[10-13] used to couple the *tert*-chloroacetylene (61) to aniline systems could also be used to couple a chloroalkyne such as (68), with side chains similar to those of virantmycin. Cyclization to (91) could then be followed by selective functionalization of the double bond, using previously reported chemistry,[10,14,22] which would result in the desired virantmycin analogue (Scheme 26, page 31).

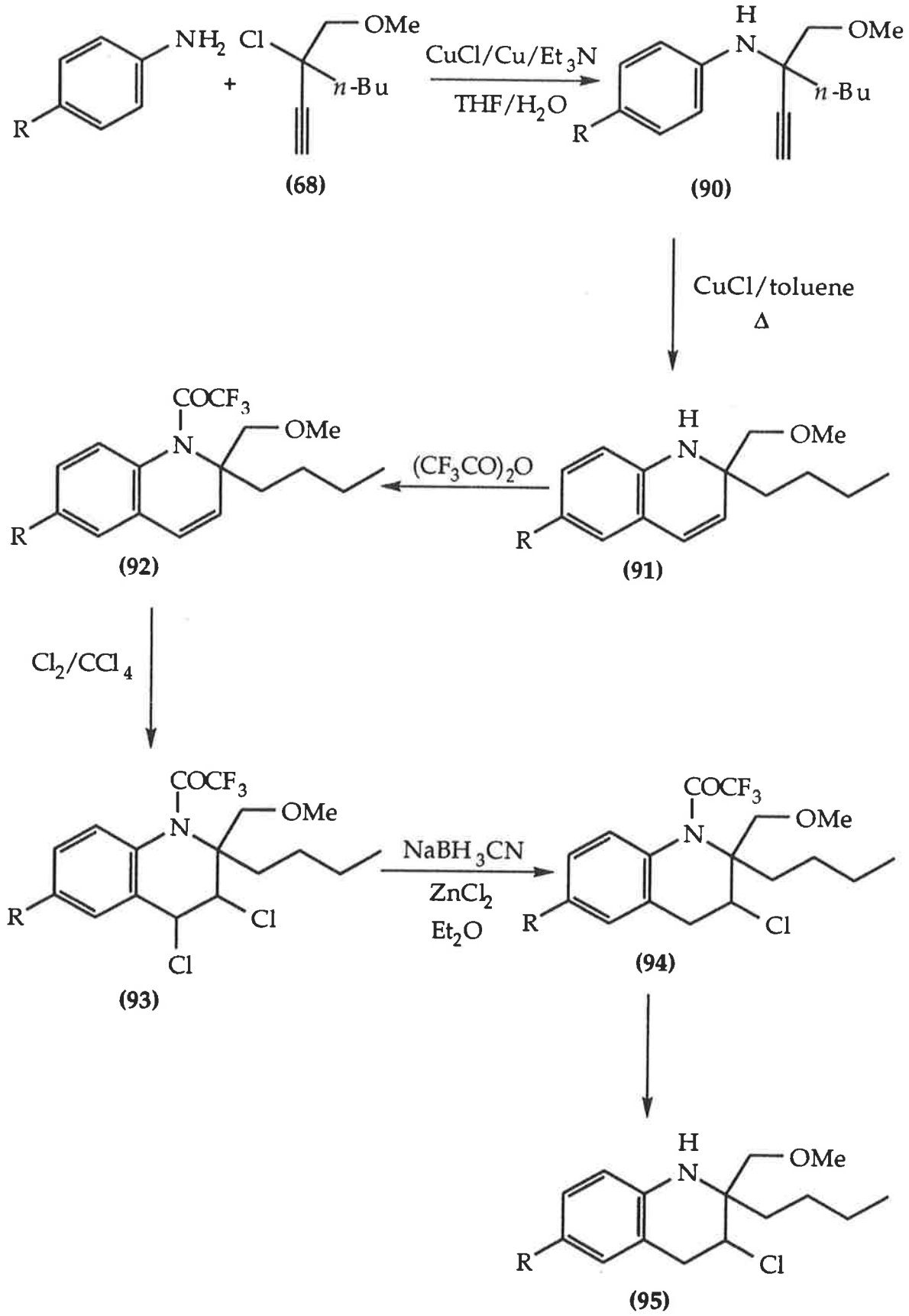
1.1 Synthesis of starting materials

1.1 (a) Preparation of tert*-chloroacetylenes*

The simple chloroalkyne (61), used as a model in order to establish appropriate experimental conditions, was synthesized in 67% yield using a literature procedure[16] (Scheme 27).



Scheme 27

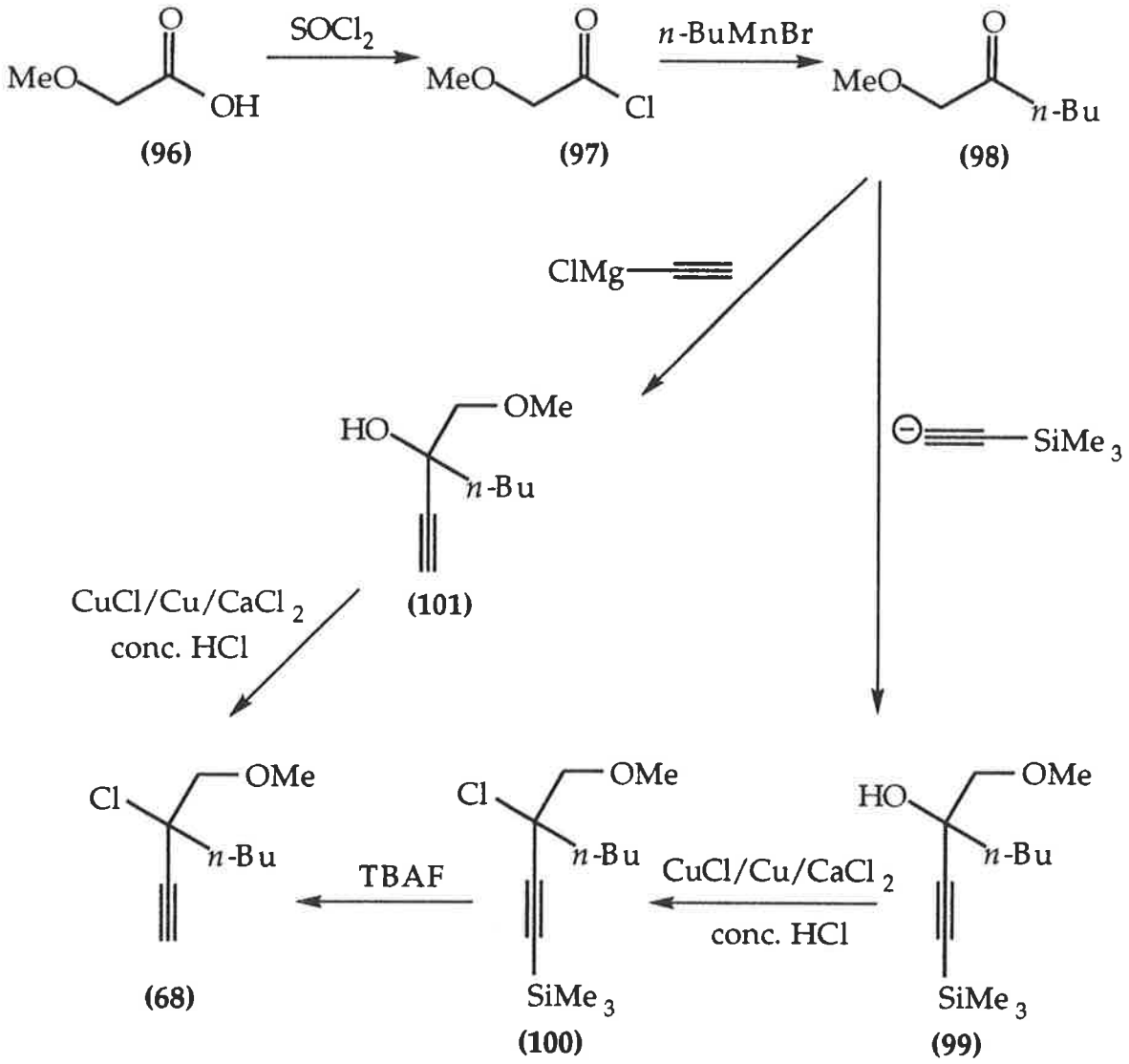

NH2
Cl
OMe
n-Bu
R
(68)
CuCl/Cu/Et3N
THF/H2O
H
N
OMe
n-Bu
R
(90)
CuCl/toluene
Δ
COCF3
N
OMe
R
(92)
(CF3CO)2O
H
N
OMe
R
(91)
Cl2/CCl4
COCF3
N
OMe
R
Cl
Cl
(93)
NaBH3CN
ZnCl2
Et2O
COCF3
N
OMe
R
Cl
(94)
H
N
OMe
R
Cl
(95)

Scheme 26

Francis[9] has reported a synthesis of the chloroalkyne (68) beginning from methoxyacetic acid (96) (Scheme 28). Conversion of methoxyacetic acid (96) to the corresponding acid chloride (97) was achieved[9] using a literature procedure.[15] Reaction of (97) with *n*-butylmanganese bromide[9,17] provided the methoxyketone (98) in moderate yield. Lithium trimethylsilylacetylide reacted readily[9] with the ketone (98) to introduce the alkyne group into the molecule, and the resulting alcohol was converted to the chloralkyne (68) by adapting previously reported chemistry.[9,16]

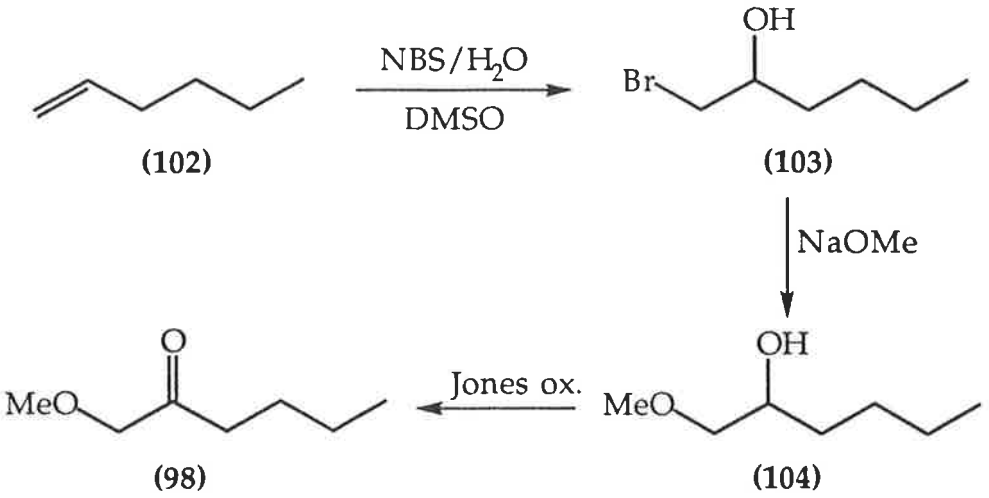
An alternative route involved the reaction of the ketone (98) with ethynylmagnesium chloride to give the acetylenic alcohol (76), which was also converted to the chloroalkyne (68)[9,16] (Scheme 28).

Attempts to reproduce these reactions were successful except in the case of the addition of *n*-butylmanganese bromide (prepared *in situ* from *n*-butylmagnesium bromide and manganese (II) iodide) to methoxyacetyl chloride (97), with yields for the reaction only poor to moderate. The use of organomanganous reagents for the controlled addition of alkyl groups to acid chlorides has been reported[17] to reduce overalkylation compared to the addition of Grignard reagents to the same system. However, overalkylated products always formed a considerable portion of the crude reaction mixture; and this work, as well as previous studies of the reaction within our group,[9] have suggested that while the application of this chemistry to our system can be successful, the reaction as a whole is unreliable.



Scheme 28

Therefore, investigations into a more efficient synthesis of the ketone (98) were undertaken. Retrosynthetic analysis indicated that the methoxyketone (98) could be obtained from a sequence of reactions beginning with 1-hexene (102) (Scheme 29).



Scheme 29

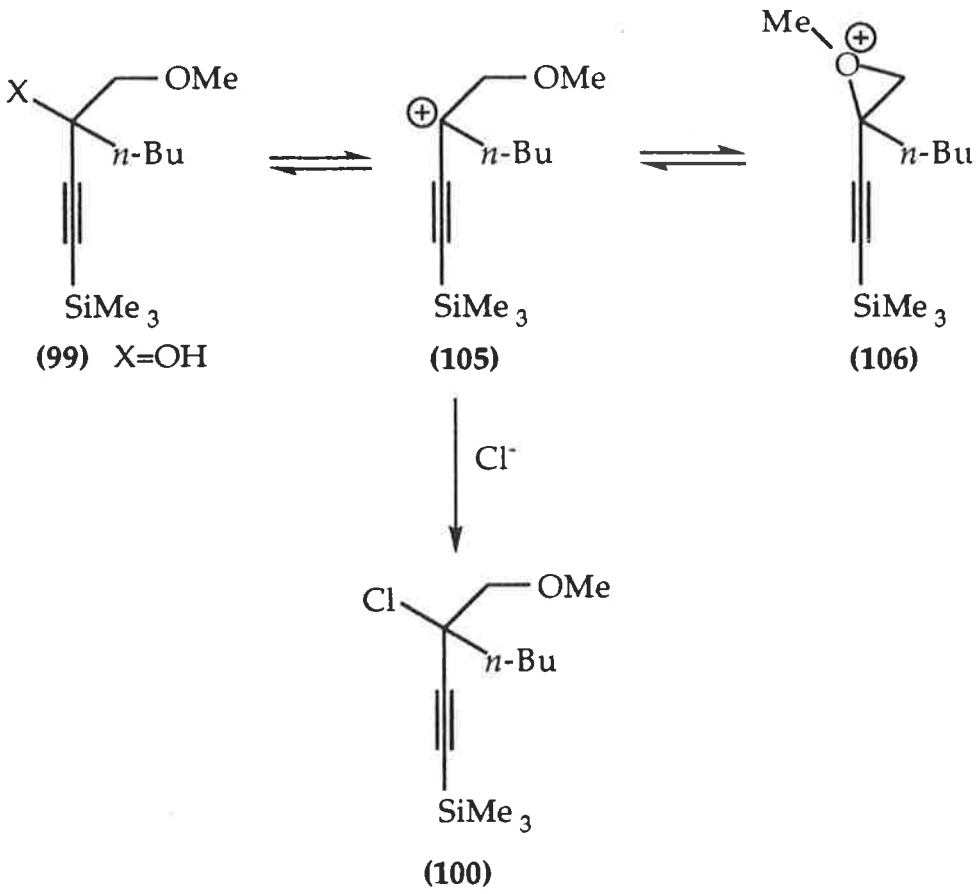
The alkene (102), when treated with N-bromosuccinimide in moist DMSO, gave the bromohydrin (103) in 96% yield, with ^{1}H nmr and mass spectral data confirming the structure of the compound. The methoxyalcohol (104) was obtained in 84% yield by treating a solution of the bromohydrin (103) with sodium methoxide. ^{1}H nmr of the product showed a singlet for the methoxy protons at δ 3.40, as well as an AB quartet at δ 3.30 for the diastereotopic methylene protons between the methoxy group and the carbon bearing the hydroxy function. A broad singlet, exchangeable with D_2O, at δ 2.73 confirmed the presence of the alcohol. Jones oxidation of the alcohol (104) provided the ketone (98) in 69% yield after purification by distillation. The ^{1}H nmr of (98) showed a singlet at δ 3.42 for the hydrogens of the methoxy group, a singlet at δ 4.03 corresponding to the protons of the methylene group between the methoxy and carbonyl groups and a triplet at δ 2.43 for the hydrogens in the other methylene group adjacent to the carbonyl carbon.

The methoxyketone (98) was then reacted with lithium trimethylsilylacetylide (formed *in situ* from trimethylsilylacetylene and *n*-butyllithium) to give the

alkynol (99) in moderate yield. A singlet at δ 3.46, corresponding to the methoxy hydrogens, was observed in the ^1H nmr spectrum of (99), as well as two doublets at δ 3.38 and 3.48 for the diastereotopic protons in the methylene group attached to the oxygen atom. A signal at δ 0.17 confirmed the presence of the trimethylsilyl group and a broad singlet at δ 2.80 that exchanged with D_2O indicated the presence of an alcohol.

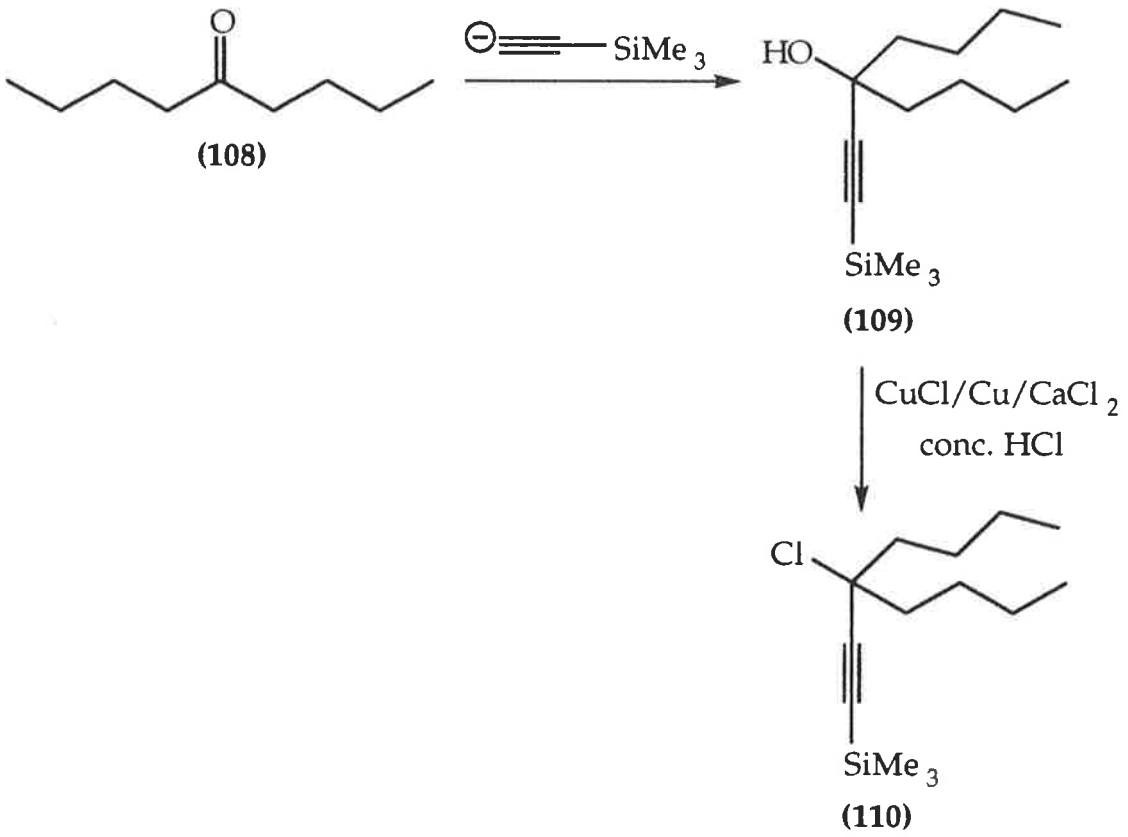
The chloroalkyne (100) was obtained in good yield by stirring the alkynol (99) with cuprous chloride, calcium chloride and copper bronze in concentrated hydrochloric acid at room temperature for 48 hours in a modification of a reported procedure.[16] The ^1H nmr of the chloroalkyne (100) showed a downfield shift in the signals for the hydrogen atoms that were previously adjacent to the hydroxy-bearing carbon in the starting material, indicating the replacement of the hydroxy group with the more electronegative chlorine atom. The hydrogens of the methylene group in the butyl chain adjacent to the carbon bearing the chlorine atom resonated further downfield to become a separate signal at δ 2.0, compared to being part of a multiplet at δ 1.3-1.7 in the starting alkynol (99). The signal for the hydrogens of the methylene group of the methoxymethyl portion moved downfield to δ 3.64 and appeared as a singlet, compared to the two doublets at δ 3.38 and 3.48 for the corresponding hydrogens in the starting material. This latter observation suggests that the hydrogens in this methylene group are, surprisingly, no longer diastereotopic.

The reaction to form (100) is thought to proceed *via* an S_N1-type mechanism[16] in which the copper helps to stabilize carbocationic and/or allenic intermediates. The carbocation (105) could also be stabilized by the oxygen in the methoxymethyl side chain, forming an oxiranium salt (106) (Scheme 30).



Scheme 30

The only product isolated from the reaction was the desired chloroalkyne (100). The increased reaction time of alkynol (99) (48 hours at room temperature compared to 1 hour at 0° for the dimethyl analogue (56)), could be due to the increase in steric bulk at the chiral centre, hindering the attack of chloride ion on a species such as (105), which is much more sterically constrained than the similar intermediate formed from the dimethyl-substituted alkynol (56). The increased reaction time also suggests that the methoxymethyl side chain of (99) has an electron withdrawing effect only, compared to the effect of the corresponding methyl group of the simpler analogue (56), and that the formation of an oxiranium species is not likely.



Scheme 31

Another look at the electronic and steric effects of the side chains was afforded by the synthesis of chloroalkyne (110) (Scheme 31) *via* a similar sequence to that used for the preparation of (100). Commercially available 5-nonanone (108) was reacted with lithium trimethylsilylacetylide at -78° to give the dibutylalkynol (109) in 85% yield. ^{1}H nmr and mass spectral data confirmed the structure of (109), with the ^{1}H nmr showing a diagnostic signal at δ 0.16 for the protons of the trimethylsilyl group and the mass spectrum showing a peak at m/z 223, corresponding to a loss of OH from the molecular ion, which was not observed. The alkynol (109) was stirred with cuprous chloride, calcium chloride and copper bronze in concentrated hydrochloric acid at room temperature for 24 hours to give the chloroalkyne (110) in 91% yield after

purification. The mass spectrum for this product showed the expected molecular ion at m/z 243/245 with a relative abundance of 3:1.

The alkynol (109) required only 24 hours at room temperature to form (110), compared with 48 hours needed to form (100). This suggests that the oxygen atom in the side chain of (99) plays some part in slowing the rate of the substitution reaction to form (100).

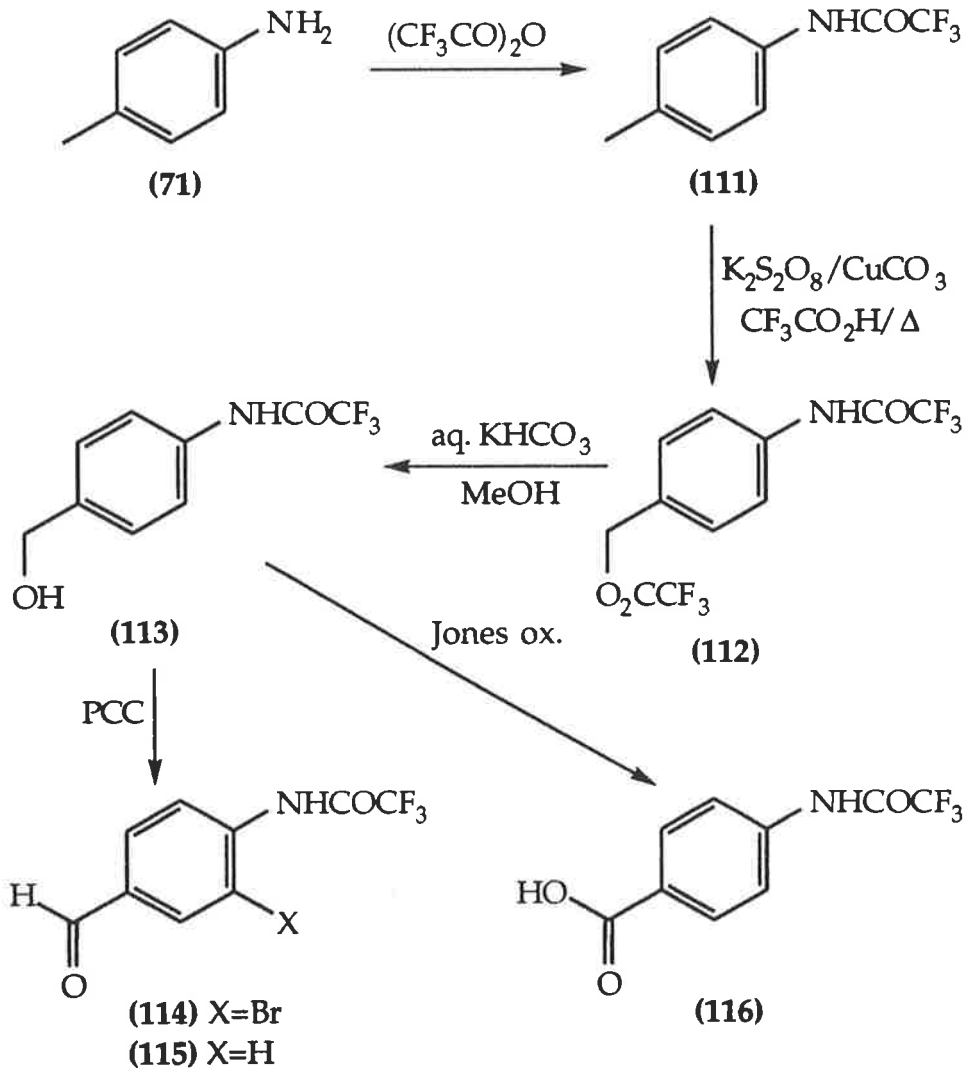
The methoxymethyl group of (100) was replaced with an *n*-butyl side chain to investigate what effect the lack of an oxygen atom in the side chain had on the reaction time in the formation of (110), as well as to study the effect of increased steric bulk in later reactions using (110). The dibutyl compound (110) removes any stereochemical problems; whereas an *n*-propyl/*n*-butyl-substituted compound, which is a closer analogue to the methoxymethyl substituted (100), does not.

1.1 (b) Preparation of aromatic nuclei

Although most of the anilines required for use in the coupling reaction[11,12,21] described in the Introduction were commercially available, some had to be synthesized.

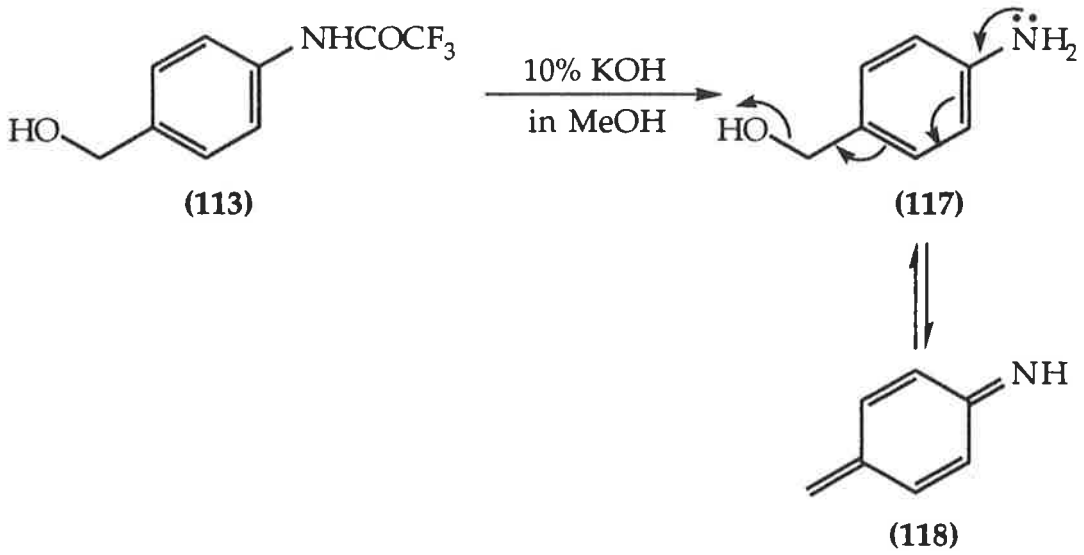
The first aromatic subunits required were the benzylic alcohol (113) and the aldehyde (115). Related systems have been synthesized by Raner[8] and Francis,[9] and a similar approach was employed here (Scheme 32).

p-Toluidine (71) was treated with trifluoroacetic anhydride to give a quantitative yield of the trifluoroacetamide (111), which was refluxed in trifluoroacetic acid with potassium persulphate and cupric carbonate to afford the amidoester (112) in 71% yield. The ^1H nmr of (112) showed a singlet at δ 5.35 for the hydrogens of the methylene group, indicating that the ester moiety had been introduced. Selective hydrolysis of the ester (112) was achieved using aqueous potassium bicarbonate in methanol to give the amidoalcohol (113) in 70% yield. The moderate yield may be due to the increased solubility of the product in water, causing some loss during workup. The ^1H nmr of (113) showed a singlet resonance at δ 4.70 for the methylene group as well as a broad singlet at δ 1.78, that exchanged with D_2O, for the hydroxyl proton.



Scheme 32

Hydrolysis of the amidoalcohol (113) to the desired aniline (117) was deferred due to the expected[72] instability of the latter, which would readily lose water to give the imine (118) (Scheme 33).

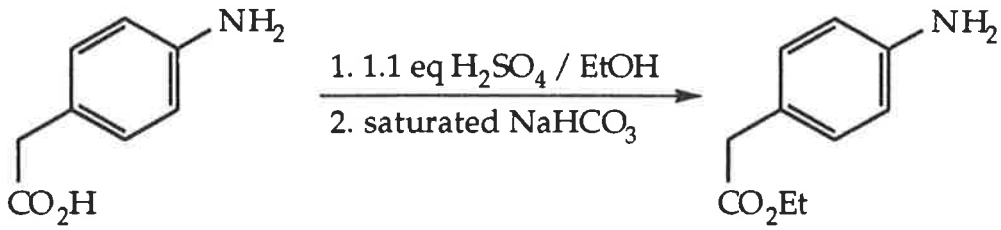


(113) **(117)** **(118)**

Scheme 33

Raner[8] reported the oxidation of the bromoalcohol (47) to the corresponding aldehyde (114) using Jones reagent. However, when this method was applied to the similar system (113), the sole product was the carboxylic acid (116) (Scheme 32), which suggests that the bromine atom present on the aromatic ring of (47) was sufficiently deactivating to prevent further oxidation of the aldehyde (114), while the absence of such an electron withdrawing group in (113) allowed complete oxidation to the carboxylic acid. Successful oxidation of the benzylic alcohol (113) to the required aldehyde (115) was achieved in quantitative yield using pyridinium chlorochromate[26] (PCC). A singlet resonance at δ 9.98 in the ^{1}H nmr of (115), corresponding to the aldehydic proton, and a molecular ion at m/z 217 in the mass spectrum confirmed the formation of the aldehyde.

4-Aminophenylacetic acid (119) was protected as the ethyl ester (120) (Scheme 34) to prevent interference of the carboxylic acid moiety in later reactions. Treatment of the acid (119) with 1.1 equivalents of concentrated sulphuric acid in refluxing ethanol followed by basic workup provided the ester (120) in a 97% yield.

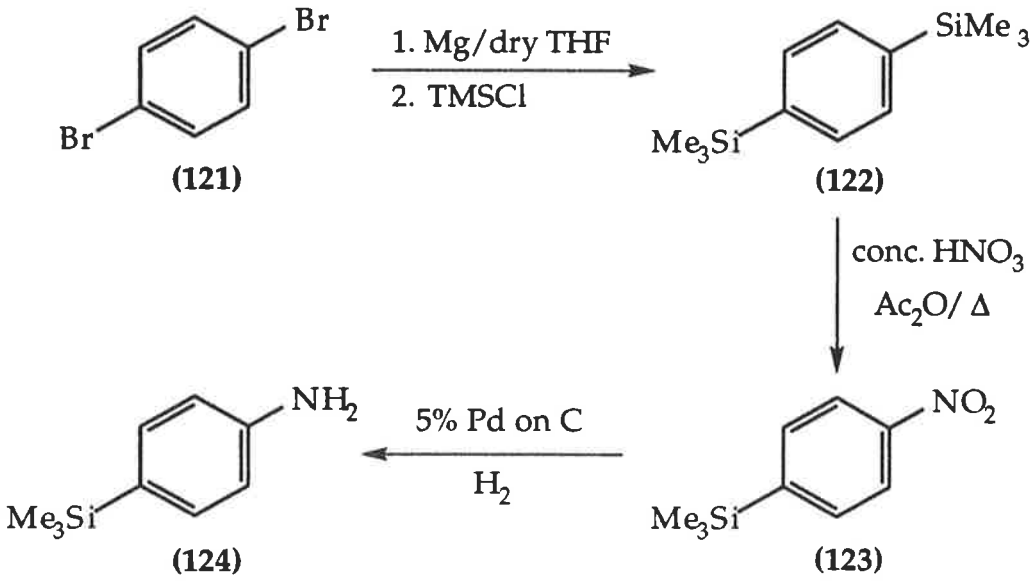


(119) **(120)**

Scheme 34

The *p*-trimethylsilyl compound (124) was synthesized as outlined in Scheme 35. The *bis*-Grignard reagent[18] formed from *p*-dibromobenzene (121) was quenched with freshly distilled trimethylsilyl chloride to yield the disilyl compound (122) after workup. Nitration of (122) was carried out by refluxing a solution of *bis*-trimethylsilylbenzene (122) in acetic anhydride with 70% nitric acid. This is in contrast with a reported procedure[24] in which a solution of fuming nitric acid in acetic anhydride was added to a solution of the disilyl compound in acetic anhydride. When the latter procedure was attempted, a violent reaction occurred between the acetic anhydride and the nitric acid when they were mixed prior to their addition to the disilyl compound. This appeared to decrease the activity of the nitrating reagent. Addition of neat, concentrated nitric acid to (122) in hot acetic anhydride avoided the premature reaction of the acid with the solvent, ensuring that any nitrating agent formed *in situ* would react in the desired manner. The nitro compound (123) was

hydrogenated[25] over 5% palladium on carbon to afford *p*-trimethylsilylaniline (124) in 65% yield.

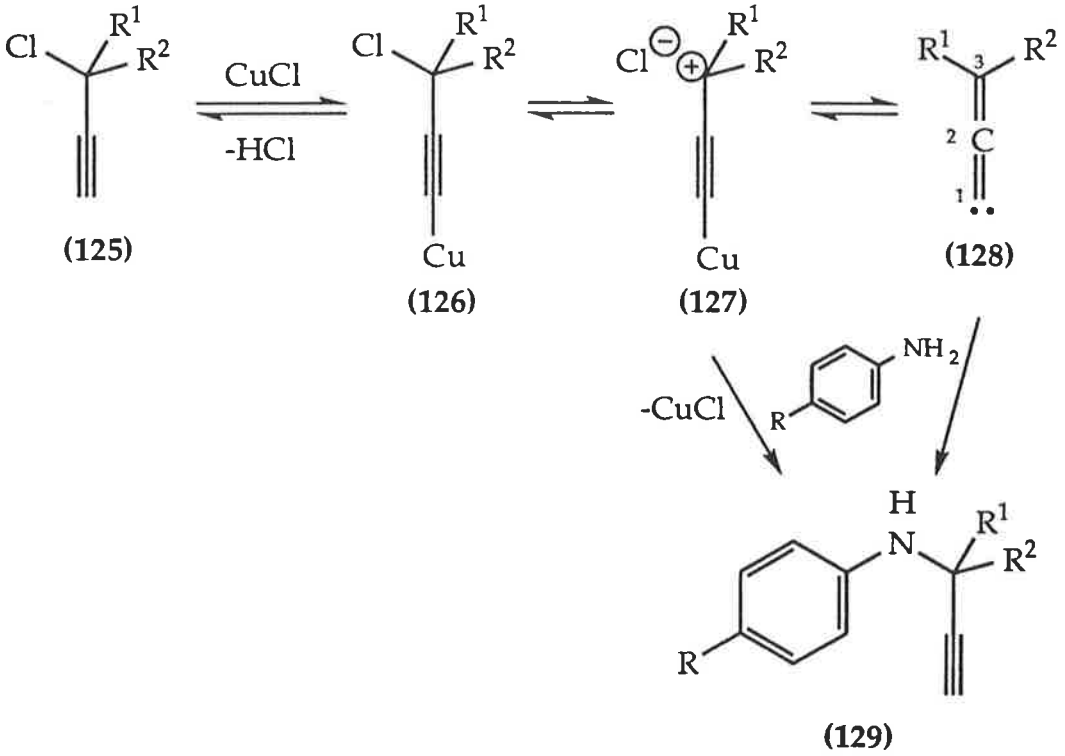


(121) (122) (123) (124)

Scheme 35

1.2 The Coupling Reaction

Alcoholysis of propargyl halides under basic conditions is known[28] to proceed *via* an S_N1-type mechanism involving zwitterionic and/or carbene intermediates. A recent paper[20] has proposed that the amination of propargyl phosphates proceeds *via* a similar mechanism. N-propargyl anilines have been synthesized from allenic precursors,[73,74] so it is possible that the coupling reaction between an aniline and a *tert*-chloroacetylene follows a mechanism such as that outlined in Scheme 36.

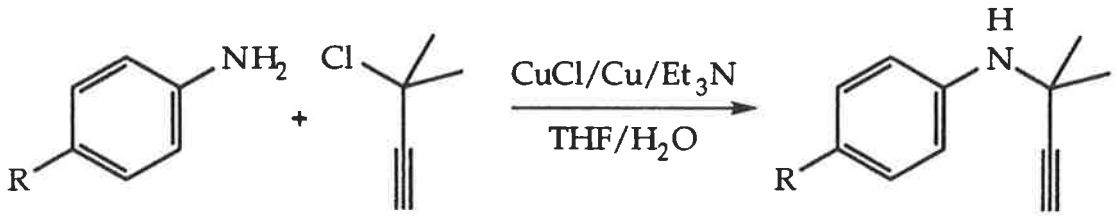


Scheme 36

The copper acetylide complex (126), formed from the reaction of (125) with cuprous chloride in the presence of a base, loses chloride ion to give the zwitterion (127) and/or the carbene (128). Nucleophilic attack by the nitrogen

atom at the C3 position of either (127) or (128) would give the desired N-propargyl aniline and regenerate the copper (I) catalyst.

Initial studies of the coupling reaction were undertaken using the dimethyl substituted chloroalkyne (61) with numerous aniline systems (Scheme 37) in order to determine the scope of the reaction and establish appropriate reaction conditions that could be used with more complicated systems.



(71) R=Me
(130) R=CO_2Et
(131) R=OMe
(132) R=Br
(133) R=NH_2
(134) R=OH
(135) R=NHAc
(124) R=$SiMe_3$
(120) R=CH_2CO_2Et
(136) R=I

(61)

(72) R=Me
(73) R=CO_2Et
(74) R=OMe
(137) R=Br
(138) R=NH_2
(139) R=OH
(140) R=NHAc
(141) R=$SiMe_3$
(142) R=CH_2CO_2Et
(143) R=I

Scheme 37

The methyl, methoxy and ester-substituted compounds (72),[10,14] (74)[14] and (73)[9,14] respectively had already been synthesized using the reported procedure[12] of stirring the aniline and the *tert*-chloroacetylene with triethylamine, cuprous chloride and copper bronze in a tetrahydrofuran/ water mixture.

Attention was then focussed on building up a large range of compounds with varying R groups on the aromatic ring for use in the cyclization reaction.[14] It was envisaged that the series should have both electron withdrawing and electron donating substituents so that a study could be made of the effect the electronic nature of the aromatic substituent on both the coupling and cyclization reactions. *p*-Halo-substituted compounds were targets due to the possibility of their being used at a later stage in palladium-catalyzed reactions. Systems with *p*-hydroxy, amino and trimethylsilyl groups were also desirable because such subsituents may be manipulated to other useful functional groups. The homo-analogue (142) was also of interest since it would allow comparison of the effects of the conjugated and non-conjugated ester groups of (73) and (142) respectively on the coupling and cyclization reactions.

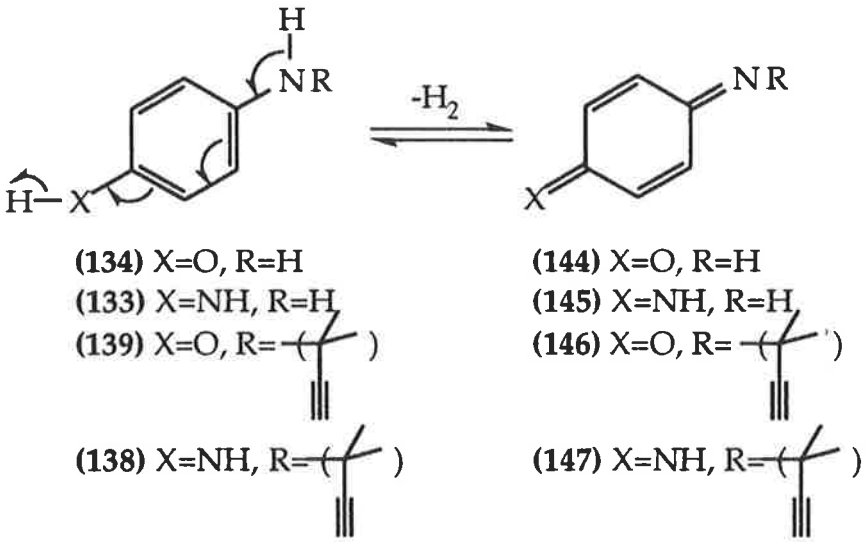
Table 1 - Substituent effect on reaction time taken to form N-substituted anilines and selected ^1H nmr data

Compound	R	Time	δ (C≡CH)
(72)	Me	30 min	2.34
(73)	CO_2Et	6 h	2.41
(74)	OMe	15 min	2.34
(137)	Br	1 h	2.38
(138)	NH_2	19 h	2.32
(139)	OH	1 h	2.34
(140)	NHAc	2 h	2.36
(141)	$SiMe_3$	45 min	2.38
(142)	CH_2CO_2Et	1.5 h	2.36
(143)	I	1 h	2.38

The N-propargyl anilines (72)-(74) and (137)-(143) were synthesized in good yields using the reported procedure[12] (Table 1). The time taken for each reaction was obtained by monitoring the reaction's progress by thin layer chromatography (tlc), with completion of the reaction being taken as the time when none of the starting aniline could be observed by this technique.

The time taken for each reaction correlates relatively favourably with the Hammett (σ) values[75] for the appropriate substituent. Electron-withdrawing substituents such as bromo, iodo and ester groups increased the reaction time and electron-donating substituents such as the methoxy group decreased the reaction time compared to the reference compound (72) with the methyl group on the aromatic ring. The homo-analogue (142) required a reaction time of 1.5 hours compared to the 6 hours required by the conjugated ester (73). This decrease in reaction time in going from a conjugated to a non-conjugated system is consistent with observations[69] made for these types of systems.

It was recognized that the hydroxy and amino substituents, although resonance electron donating, could lead to increased reaction times due to the tendency of the aminophenol and phenylenediamine systems to complex to the copper salts. Another problem anticipated with these systems was their oxidation to quinone-type compounds such as (144)-(147) (Scheme 38). However, it was hoped that the N-substituted products (138) and (139) would be stable enough to allow studies of their behavior towards the cyclization conditions.



(134) X=O, R=H
(133) X=NH, R=H
(139) X=O, R=
(138) X=NH, R=

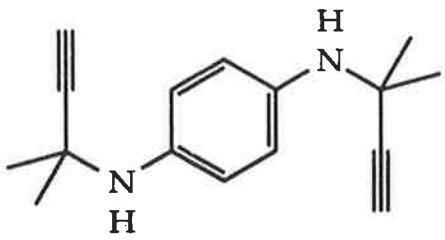
(144) X=O, R=H
(145) X=NH, R=H
(146) X=O, R=
(147) X=NH, R=

Scheme 38

The hydroxy substituted N-propargyl aniline (139) was obtained in 59% yield from the reaction of *p*-aminophenol (134) and the chloroalkyne (61) after a reaction time of 1 hour (Table 1). The presence of a broad absorption between 2500 and 3300cm^{-1} in the infrared spectrum of the product suggested that an acidic hydrogen was still present in the molecule. This indicated that the phenol moiety was intact, thus suggesting N-alkylation. Although the presence of an electron donating moiety such as the hydroxyl group would be expected to facilitate the coupling reaction, the increased reaction time may be due to complexation of the copper salts with the phenol portion of the molecule. The accelerating effect on the reaction time of an electron donating substituent has been demonstrated[14] by the methoxy substituted system (131), which undergoes the coupling reaction in 15 minutes. The latter system is less prone to complexation than the related (134) since the oxygen atom is not present as a phenol, therefore the benefits of the electron donating oxygen atom in (131) are able to be seen without the interference of either

complexation or oxidation. The lower yield may be attributed to product loss due to the formation of iminoquinone species such as those shown in Scheme 38 (X=O).

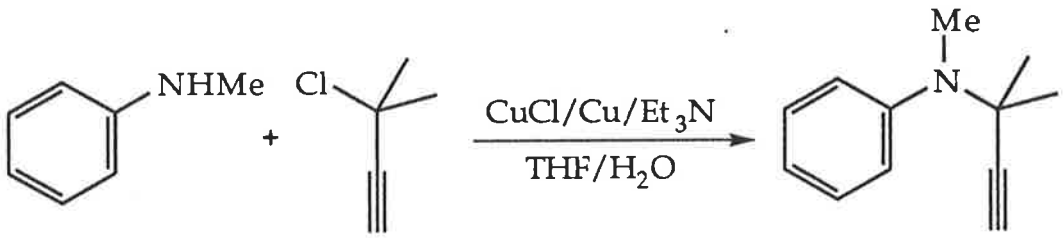
The reaction between *p*-phenylenediamine (133) and the chloroalkyne (61) was hampered by the appearance of a black precipitate when the copper salts were added to a solution of the diamine in tetrahydrofuran/water. This precipitate was presumed to be the copper complex formed from the diamine (133) and cuprous chloride/copper bronze. The reaction was stirred for 19 hours and after workup, two products were isolated by flash column purification. The major product was the desired amino substituted N-propargyl aniline (138) (Table 1), obtained in 25% yield. The other product, isolated in a 5% yield, was the dialkylated aniline (148), whose simple ^{1}H nmr spectrum, consisting of four singlets, reflected its symmetry. Signals at δ 1.54, 2.34, 3.0 and 6.90 represented the four methyl groups, two acetylenic hydrogens, two amine hydrogens and the aromatic hydrogens respectively. The long reaction time may be attributed to the reduced reactivity of the diamine system due to copper complexation, while the reduced yield may be due to the formation of iminoquinone species (as for the hydroxyaniline system) (Scheme 38, X=NH).



(148)

The *p*-substituent is likely to affect the rate of the coupling reaction by altering the nucleophilicity of the amino group. Deactivating substituents such as esters and halogens would reduce the nucleophilicity of the nitrogen atom by delocalizing the lone pair of electrons to varying extents, while an activating substituent such as a methoxy group would be able to increase the nitrogen atom's nucleophilicity by donating electrons into the π-system of the aromatic ring.

Also investigated was the coupling reaction between N-methyl aniline (149) and the chloroalkyne (61) (Scheme 39).

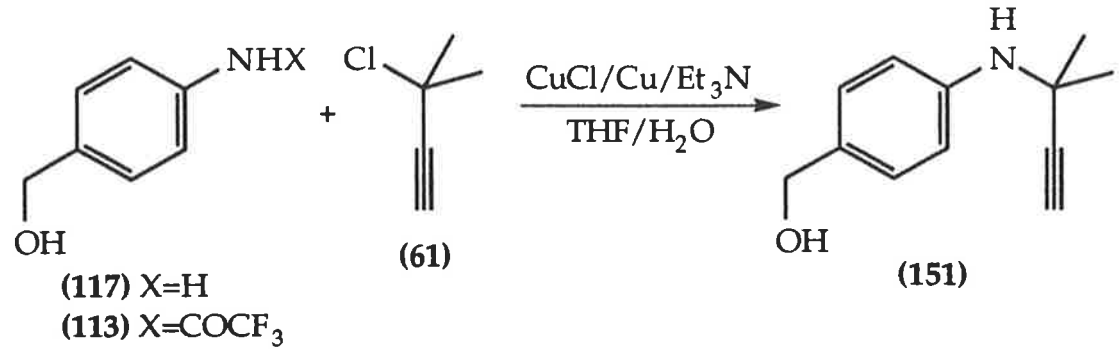


(149) (61) (150)

Scheme 39

The N-methyl-N-propargyl aniline (150) was isolated in a 24% yield and exhibited spectral data consistent with its structure. The reduced yield and extended reaction time of 2 hours was consistent with the introduction of more steric bulk around the nitrogen atom, which would hinder its attack of the intermediate formed from the chloroalkyne (61) (Scheme 36), thereby slowing the rate of the coupling reaction.

Another system desired for this study was the N-propargyl aniline (151), formed from the reaction of the aminoalcohol (117) and the chloroalkyne (61) (Scheme 40).



(117) X=H
(113) X=$COCF_3$

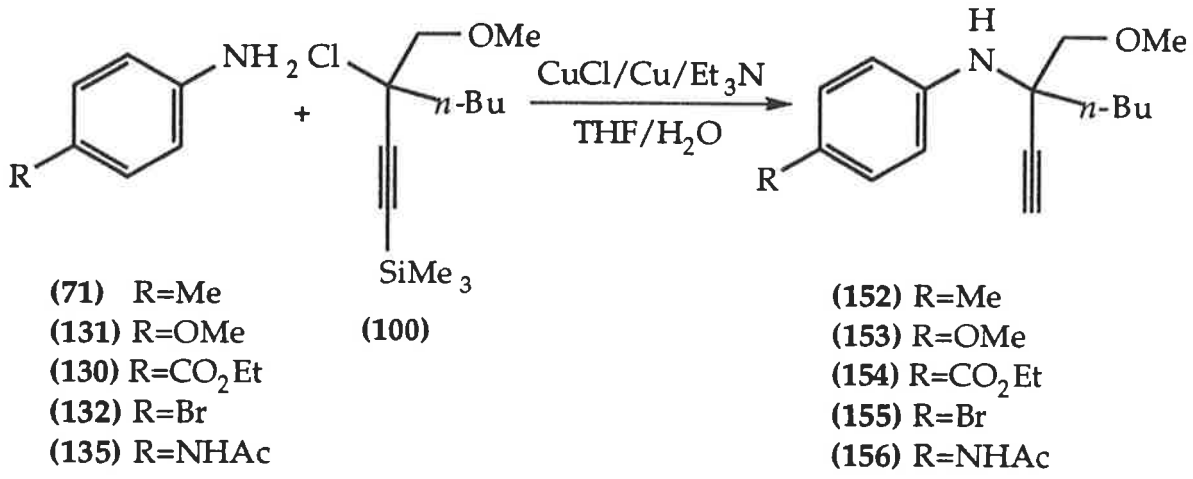
(61)

(151)

Scheme 40

It was expected that aniline systems such as (117) might be unstable due to the potential for the loss of water from the molecule, giving rise to the imine (118) (Scheme 33, Chapter 1.1 (b)). The amidoalcohol (113), however, is a stable molecule due to the deactivating effect of the trifluoroacetyl group, which delocalizes the lone pair of electrons on nitrogen, thus making the formation of imine (118) less favourable. Therefore, initial investigations involved the use of the trifluoroacetamide (113). It was anticipated that the basic conditions of the coupling reaction would slowly hydrolyze the amide (113) to the free aniline (117), which would in turn couple to the chloroalkyne (61), driving the position of equilibrium to the right. Unfortunately, subjection of amidoalcohol (113) and chloroalkyne (61) to the coupling conditions for 48 hours at reflux afforded only starting materials after chromatography. From this result, it was concluded that the aqueous triethylamine conditions used in the coupling reaction were not strong enough to effect the required hydrolysis of amide (113). Studies of the aminoalcohol (117) were not pursued, since previous work[72] has shown that the latter system is very unstable, losing water to give the imine (118) (page 41).

Having established that the coupling reaction works well for a wide variety of different R groups with the dimethyl substituted chloroalkyne (61), further investigations were directed towards coupling reactions involving the methoxymethyl/*n*-butyl substituted chloroalkyne (100) and various *p*-substituted anilines (Scheme 41).



(71) R=Me
(131) R=OMe
(130) R=CO_2Et
(132) R=Br
(135) R=NHAc

(100)

(152) R=Me
(153) R=OMe
(154) R=CO_2Et
(155) R=Br
(156) R=NHAc

Scheme 41

The coupling reaction between *p*-toluidine (71) and chloroalkyne (100) has been achieved,[9] but only in moderate yields, so a number of conditions were tested in attempts to optimize the yield of the N-substituted aniline (152) (Table 2).

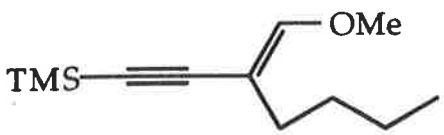
Stirring the reactants at room temperature for 1.5 hours under the originally reported conditions[9-13] gave a low yield of the coupled product (152). After 24 hours at reflux, tlc indicated that a small amount of the desired N-propargyl aniline was present, but significant amounts of baseline material and a weakening in the intensity of the chloroalkyne spot suggested decomposition of the latter was also occurring.

Table 2 - Reaction conditions and results for the reaction of (71) and (100)

Reaction conditions	Yield/Result
CuCl/Cu/Et_3N/THF/H_2O/RT/1.5h	20%
CuCl/Cu/Et_3N/THF/H_2O/RT/24h	61%
CuCl/Cu/Et_3N/THF/H_2O/Δ/3h	Chloroalkyne decomposition
CuCl/Cu/Et_3N/THF/Δ/3h	No reaction
CuCl/Cu/Et_3N/dioxane/H_2O/Δ/5h	Chloroalkyne decomposition

A higher reflux temperature, achieved by using dioxane as solvent, and a shorter reaction time were used in the hope that the shorter reaction time would reduce chloroalkyne decomposition and the higher reflux temperature would facilitate the coupling. However, tlc again showed mostly baseline material, suggesting decomposition of the chloroalkyne (100).

The thermal stability of the chloroalkyne (100) was investigated by heating it with triethylamine in deuterochloroform for 3 hours under nitrogen, with the mixture transferred directly to an nmr tube. ^1H nmr showed only peaks for triethylamine and unreacted chloroalkyne (100), with no evidence of the conjugated product (157). Therefore, it was concluded that it was unlikely that elimination to give (157) was taking place under the reaction conditions.



(157)

Tlc of a reaction using the same initial coupling conditions, but without any water, indicated that no reaction had occurred after 3 hours at reflux. This result suggested that water is required in the reaction mixture in order for the coupling reaction to take place, which is not unreasonable, since an S_N1 process would be favoured by the presence of a protic solvent.

When the original reaction conditions (cuprous chloride, copper bronze and triethylamine in tetrahydrofuran and water, stirring at room temperature) were used and the reaction time extended to 24 hours, the N-propargyl aniline (152) was obtained in a 61% yield after purification. The product (152) showed an AB quartet at δ 3.48 and 3.55 in its ^1H nmr spectrum, attributable to the two diastereotopic methylene hydrogens in the methoxymethyl side chain. A singlet resonance at δ 2.42 was assigned to the acetylenic hydrogen. No evidence of a signal for the trimethylsilyl group was seen; previous studies[9] of coupling reactions with the chloroalkyne (100) have reported that the trimethylsilyl group is lost under the coupling conditions, so the absence of a trimethylsilyl signal was not unexpected. The longer reaction time of 24 hours for *p*-toluidine (71) and the chloroalkyne (100) (compared with the 1 hour taken when *p*-toluidine was reacted with the chloroalkyne (61)) can be rationalized in a similar fashion to that of the formation of the chloroalkyne (100) (see Chapter 1.1 (a)). Assuming that the coupling reaction proceeds *via* an S_N1-type mechanism similar to that shown in Scheme 36, one cause of the increased reaction time could be the increase in steric bulk around the chlorine atom. After ionization (Scheme 36), attack of the nitrogen atom on either one of the two intermediates (127) or (128) (formed from (125), where $R^1=CH_2OCH_3$ and $R^2=n$-Bu) would be more difficult than attack on the intermediates formed from the chloroalkyne (61) (where $R^1=R^2=CH_3$), therefore, the reaction time would be expected to increase.

Reaction of ethyl-4-aminobenzoate (130) with the chloroalkyne (100) (Scheme 41) provided the coupled product (154) in a moderate yield of 41%, even after an extended reaction time of 72 hours. The reduced yield and longer reaction time were attributed to a combination of the increased steric bulk of the chloroalkyne (100) and the electron withdrawing effect of the ester group of (130) rendering the nitrogen less nucleophilic. The product (154) showed an AB quartet centred at δ 3.58 in its ^{1}H nmr spectrum, which was assigned to the two diastereotopic hydrogens of the methylene group in the methoxymethyl side chain.

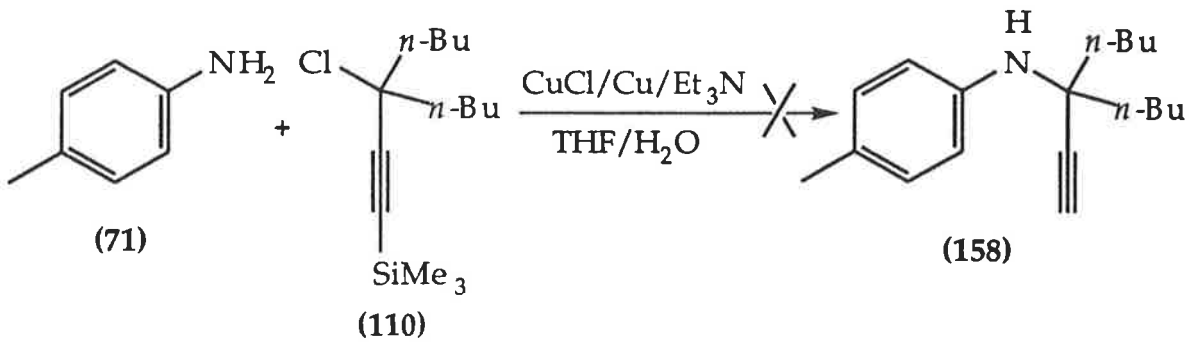
The chloroalkyne (100) was also reacted with *p*-bromoaniline (132) (Scheme 41) to give the bromo substituted coupled aniline (155) in moderate yield after a reaction time of 26 hours. Again, the reduced yield and extended reaction time can be attributed to the steric bulk of (100) and the electron withdrawing nature of the aromatic substituent. The N-propargyl aniline (155) showed the expected AB quartet at δ 3.53 in its ^{1}H nmr spectrum for the methylene hydrogens in the methoxymethyl side chain and a molecular ion at m/z 309/311 in its mass spectrum.

The coupling of *p*-aminoacetanilide (135) and the chloroalkyne (100) (Scheme 41) to give the N-substituted aniline (156) was achieved after a reaction time of 24 hours. Although the higher yield (69%) of (156) seems to conflict with previous observations of the effect of electron withdrawing aromatic substituents, the nitrogen of the amide group is also resonance electron donating; which, based on experience with the dimethyl substituted analogues, should help to increase the yield. The shorter reaction time (compared to the ester (154)) may also be explained by the ability of the amide group to act as an electron donor. The electron-withdrawing and electron-donating effects of the amide group have been reported[70] as being almost identical. This would result in the two opposing effects virtually cancelling

each other out, rendering the amido substituent approximately as electronically active as a methyl group, which appears to be the case here, since the reaction times for the methyl and amido substituted systems (152) and (156) respectively are almost exactly the same. It is interesting to note that this electronic "cancellation" effect is not observed for the reaction to form the corresponding 2,2-dimethyl substituted system (140) (see Table 1, page 46). This suggests that, for the reactants shown in Scheme 41, the steric effects of the larger side chains of (100) may override the electronic effect of the *para*-aromatic substituent on the rate of the coupling reaction.

Reaction of *p*-anisidine (131) with the chloroalkyne (100) gave the N-propargyl aniline (153) after a reaction time of 2.5 hours. This is a clear indication of how an electron donating substituent on the aromatic ring facilitates the coupling reaction. The product (153) showed the AB quartet common to all of these N-substituted compounds at δ 3.47 in its ^{1}H nmr spectrum, and a molecular ion at m/z 261 in the mass spectrum.

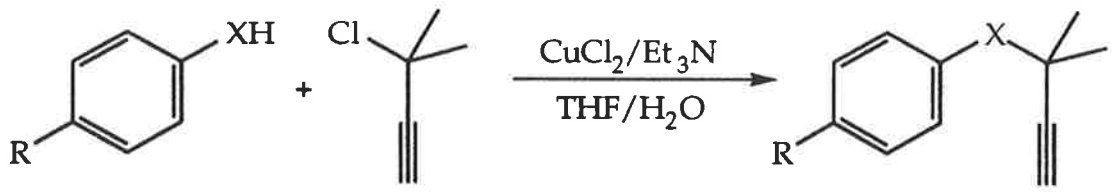
Also of interest in this study was the coupling reaction of an aniline such as (71) with the dibutyl substituted chloroalkyne (110) (Scheme 42).



(71) (110) (158)

Scheme 42

However, attempts to couple *p*-toluidine (71) with the chloroalkyne (110) were unsuccessful. Tlc of the reaction mixture after 24 hours at reflux indicated negligible product formation, and the starting materials (71) and (110) were recovered after workup. From this result, it was concluded that while the lack of an oxygen atom in the side chain appears to speed up the formation of the chloroalkyne (110) (see Chapter 1.1 (a)), the steric effect of the two bulky butyl groups hinders the reaction between chloroalkyne (110) and *p*-toluidine (71) to such an extent that no coupling occurs even after 24 hours at reflux.



(159) X=O, R=CN
(71) X=NH, R=Me

(61)

(160) X=O, R=CN
(72) X=NH, R=Me

Scheme 43

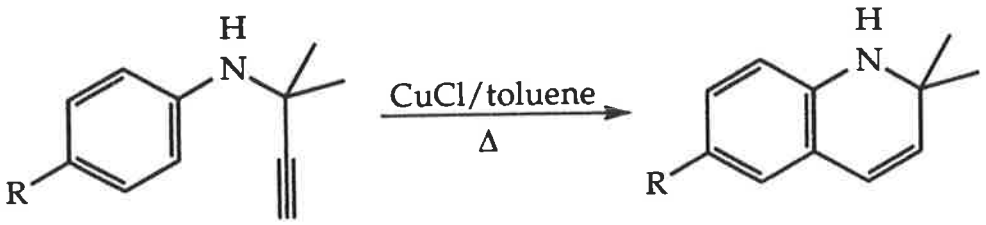
A recent paper[29] has reported the coupling of phenols such as (159) and propargyl chlorides using cupric chloride as a catalyst (Scheme 43, X=O). This method is in direct contrast to the reported methods for coupling aniline[10-13] and phenol[81] systems with *tert*-chloroacetylenes using cuprous halide salts. Therefore, it was of interest to investigate the applicability of the above phenol procedure to the coupling of anilines with propargyl chlorides. A mixture of *p*-toluidine (71), chloroalkyne (61), cupric chloride, triethylamine, tetrahydrofuran and water was stirred at room temperature for 2.5 hours (Scheme 43, X=NH). ^{1}H nmr of the crude reaction product indicated that the desired N-propargyl aniline (72) had formed, but was part of a mixture with

several other compounds. Therefore, the method using cuprous chloride was retained, since this procedure provided a cleaner route to the desired N-substituted aniline systems.

Having synthesized a wide range of N-propargyl anilines, their behaviour towards the conditions of the cyclization[14] was then investigated.

Chapter 2 - The Cyclization Reaction

The first series of compounds studied in the cyclization reaction were those with two methyl substituents α- to the nitrogen atom (Scheme 44).



(72) R=Me
(73) R=CO_2Et
(74) R=OMe
(137) R=Br
(138) R=NH_2
(139) R=OH
(140) R=NHAc
(141) R=$SiMe_3$
(142) R=CH_2CO_2Et
(143) R=I
(161) R=$OSiMe_3$

(70) R=Me
(162) R=CO_2Et
(163) R=OMe
(164) R=Br
(165) R=NH_2
(166) R=OH
(167) R=NHAc
(168) R=$SiMe_3$
(169) R=CH_2CO_2Et
(170) R=I
(171) R=$OSiMe_3$

Scheme 44

The compounds listed in Scheme 44 have a wide range of *p*-substituents, both electron withdrawing and electron donating, and it was an aim of this study to carry out a more detailed examination of the effect of electron withdrawing and donating substituents on the cyclization reaction (the initial study[14,80] was discussed in the Introduction). It was also of interest to see whether any substituents were sufficiently deactivating to prevent cyclization.

Compounds (70), (162) and (163) have been previously synthesized[10,14,80] and a check reaction using the N-propargyl aniline (74) provided the dihydroquinoline (163) in a 50% yield with spectral characteristics consistent with those reported.[14] The dihydroquinoline system is readily identified by tlc due to its intense fluorescence when compared to the starting alkyne, which enabled easy monitoring of the progress of the cyclization reaction.

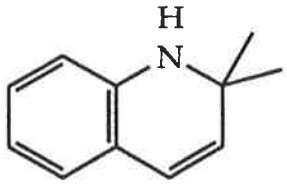
Table 3 - Substituent effects on the cyclization reaction and selected ^1H nmr data for the resulting dihydroquinolines

Compound	R	Reaction time	δ (CH=CH)
(70)	Me	1 h[14]	5.46, 6.22
(162)	CO_2Et	16 h[14]	5.40, 6.30
(163)	OMe	20 min	5.45, 6.20
(171)	$OSiMe_3$	30 min	5.50, 6.20
(169)	CH_2CO_2Et	30 min	5.46, 6.23
(167)	NHAc	45 min	5.48, 6.15
(164)	Br	2 h	5.49, 6.18
(170)	I	2 h	5.46, 6.15
(168)	$SiMe_3$	2 h	5.45, 6.39

The results of the cyclization reactions attempted are shown in Table 3. As for the coupling reaction (see Chapter 1.2), a general trend emerged in that deactivating substituents such as halogens increased the reaction time compared to the reference compound (72), while activating substituents such as methoxy[71] and trimethylsilyloxy groups decreased the reaction time.

The cyclization of the homo-analogue (142) is a good example of how the rate of cyclization can be accelerated when an electron withdrawing substituent becomes further removed from the aromatic ring. The N-propargyl aniline (73), which has an ester moiety substituted directly on the aromatic ring, required a 16 hour reaction time[14,80] for complete cyclization to the dihydroquinoline (162), whereas the homo-analogue (142) underwent complete conversion to the dihydroquinoline (169) in 30 minutes.

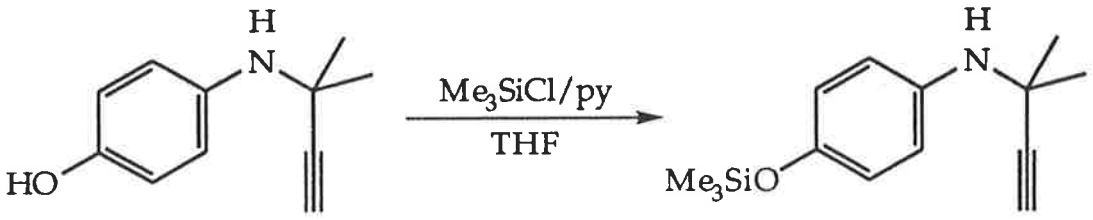
The reaction to form the *p*-trimethylsilyl substituted dihydroquinoline (168) was not as straightforward as other cyclization reactions. Two products were isolated from the flash column used to purify the crude reaction mixture. The first was the desired trimethylsilyl substituted dihydroquinoline (168), while the second product was identified by ^{1}H nmr and mass spectral data as the unsubstituted dihydroquinoline (172), formed from the hydrolysis of the trimethylsilyl group of (168) under the reaction conditions.



(172)

The unsubstituted compound (172) showed the two doublets expected of the dihydroquinoline system at δ 5.46 and 6.26 in the ^{1}H nmr spectrum, but the aromatic region had increased in complexity and the spectrum lacked a signal for the hydrogens of the trimethylsilyl moiety. The mass spectrum showed a peak at m/z 159, corresponding to the molecular ion expected for the dihydroquinoline (172).

Formation of the hydroxy substituted dihydroquinoline (166) proceeded *via* a longer route, since subjection of the hydroxy substituted compound (139) to the cyclization conditions resulted in an intractable mixture, due to iminoquinone formation as discussed in Chapter 1.2 (see Scheme 28).



(139) (161)

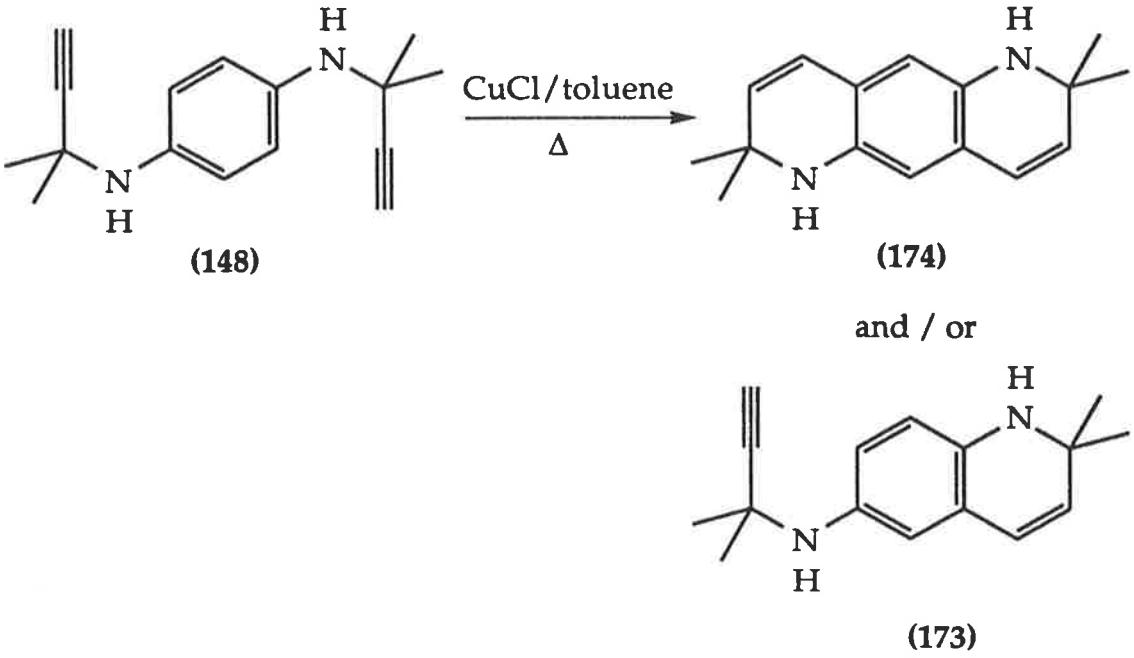
Scheme 45

The hydroxyl group was protected as a trimethylsilyl ether by treatment of a solution of (139) in tetrahydrofuran and pyridine with trimethylsilyl chloride (Scheme 45). O-protection was confirmed by infrared analysis; the broad OH peak present in the infrared spectrum of the starting material (139) was absent in the infrared spectrum of the product (161), which showed an NH absorption at 3275 cm^{-1}. The ^1H nmr of (161) exhibited a signal at δ 0.23, assigned to the hydrogens of the trimethylsilyl group. Preferential reaction at the oxygen atom was, in this case, attributed to the steric hindrance of the nitrogen atom.

Cyclization of the protected compound (161) proceeded smoothly to give the trimethylsilyloxy substituted dihydroquinoline (171). Removal of the trimethylsilyl group was found to be unnecessary at this stage, since the silyl ether was hydrolyzed under the conditions used to trifluoroacetylate the nitrogen atom (see Chapter 3).

The amino substituted aniline (138), when subjected to the cyclization conditions, gave a black precipitate (presumably a copper complex) when cuprous chloride was added to a solution in toluene. After a 2.5 hour reflux time, tlc and ^1H nmr indicated an extremely complex mixture in which the desired dihydroquinoline (165) could not be detected. This result was not unexpected, as (138) is a similar system to the hydroxy substituted (139), which also gave problems during the cyclization. Therefore, it was concluded that iminoquinone formation was causing the same problems for the amino substituted (138) as it was for (139) (see Scheme 28, Chapter 1.2). Because of this complication, it was decided not to pursue the amino substituted route any further. Since the amide (167) was successfully synthesized, further investigations of the *p*-phenylenediamine system focussed on this more stable derivative.

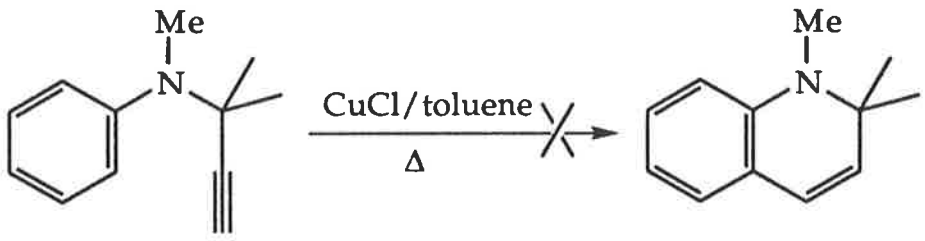
The behaviour of the dialkyne (148) towards the cyclization conditions was also studied (Scheme 46). However, after a reaction time of 5 hours, tlc and ^1H nmr indicated an extremely complex product mixture, which showed no signals that could be attributed to the olefinic hydrogen atoms expected for either the mono- or dicyclized compounds (173) and (174) respectively. Therefore, studies of the dialkyne system were discontinued.



(148) (174) (173)

Scheme 46

The cyclization of the N-methyl compound (150) to the dihydroquinoline (175) was also investigated (Scheme 47).

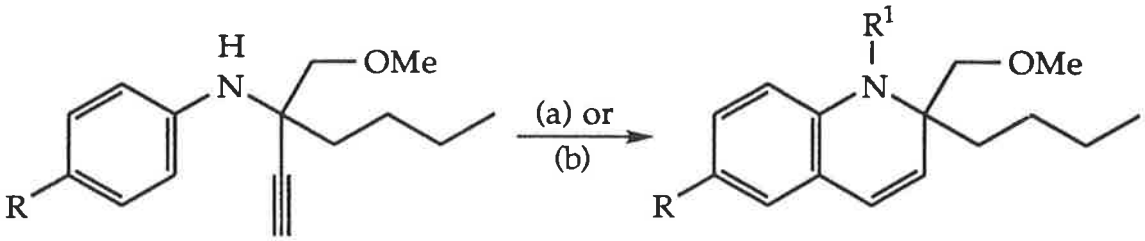


(150) (175)

Scheme 47

After a reaction time of 75 minutes, no cyclization was observed by either tlc or ^{1}H nmr. This result is consistent with the mechanism proposed in the Introduction (Scheme 15), which requires the nitrogen atom to possess a hydrogen atom for cyclization to occur.

The next series studied was one where all the compounds possessed methoxymethyl and *n*-butyl substituents α-to the nitrogen atom (Scheme 48).



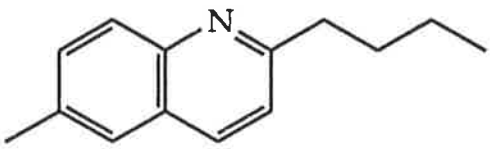
(152) R=Me
(153) R=OMe
(154) R=CO_2Et
(155) R=Br
(156) R=NHAc

(176) R=Me, R^1=H
(177) R=Me, R^1=$COCF_3$
(178) R=OMe, R^1=$COCF_3$
(179) R=CO_2Et, R^1=$COCF_3$
(180) R=Br, R^1=$COCF_3$
(181) R=NHAc, R^1=$COCF_3$

(a) CuCl/toluene/Δ
(b) 1. CuCl/toluene/Δ
2. $(CF_3CO)_2O$

Scheme 48

The methyl substituted compound (152) was cyclized (Scheme 48, conditions (a)) to the corresponding dihydroquinoline (176), with the ^{1}H nmr spectrum of the product showing the expected two alkene doublets at δ 5.28 and 6.32. However, the free dihydroquinoline (176) was found to be very unstable, readily losing dimethyl ether to give the quinoline (182).



(182)

This behaviour has been observed[2,4] previously in a similar system (6); the problem was overcome in that case by converting the free dihydroquinoline to a more stable N-formyl derivative. A similar approach was used here, by adapting the cyclization procedure (Scheme 48, conditions (b)): the cyclization method of cuprous chloride in refluxing toluene was retained, but the reaction was carried out under an atmosphere of nitrogen, and after cooling, trifluoroacetic anhydride was added under an atmosphere of nitrogen directly to the crude reaction mixture. After workup and careful chromatography, this method provided the N-trifluoroacetyldihydroquinoline (177) in 63% yield. The product (177) showed, in the ^{1}H nmr spectrum, doublets at δ 5.81 and 6.49 for the two hydrogens on the newly-formed double bond, and an AB quartet centred at δ 3.95 for the two hydrogens of the methylene group in the methoxymethyl side chain. The mass spectrum showed a molecular ion at m/z 342, corresponding to an M+H peak for the N-trifluoroacetyldihydroquinoline (177).

Since this last cyclization method was successful, it was adopted for use for all cyclizations involving compounds with the larger methoxymethyl and *n*-butyl side chains.

The methoxy-substituted alkyne (153) was cyclized to the corresponding N-trifluoroacetyldihydroquinoline (178) in 60% yield. The ^{1}H nmr spectrum of (178) showed the expected doublets for the alkene hydrogens at δ 5.88 and 6.50

and an AB quartet centred at δ 3.95 for the two hydrogens of the methylene group in the methoxymethyl side chain.

Complications were encountered in the cyclization reactions for the ester, bromo and amido substituted compounds (154), (155) and (156) respectively. After subjecting these compounds to the modified cyclization conditions, all that was recovered after workup were mixtures of varying complexity that did not contain any of the desired dihydroquinoline as evidenced by the absence of the doublets expected for the alkene hydrogens in the ^1H nmr spectrum. As it was possible that the trifluoroacetylation step was a complication, a test reaction was carried out on (154) whereby the latter was treated with cuprous chloride in refluxing toluene and the trifluoroacetylation step omitted. After 48 hours at reflux, workup of the reaction mixture gave a crude product that corresponded by tlc and ^1H nmr to a mixture of the starting material (154) and several minor products that were not formed in sufficient amounts to enable isolation and characterization. The ^1H nmr spectrum of the crude mixture also lacked signals in the olefinic region, suggesting no dihydroquinoline formation. This test reaction was repeated for (155) and (156) and provided a similar result for both. A common feature among (154)-(156) is that all three have electron withdrawing groups of varying strength. Therefore, it appears that the electron withdrawing capability of the aromatic substituents combined with the increased steric bulk of the larger side chains (compared with previous reactions with two methyl groups adjacent to the nitrogen atom) are enough to prevent cyclization.

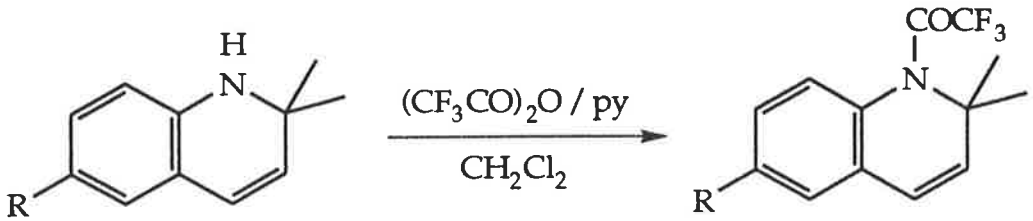
This expanded study of the cyclization reaction supports the brief study[14] previously undertaken; namely that electron donating groups facilitate the cyclization reaction and electron withdrawing groups retard it. This is especially true for the systems with 2,2-dimethyl substituted centres α- to the nitrogen atom. It also shows that the cyclization reaction is tolerant of 2-*n*-

butyl-2-methoxymethylsubstituted systems, but cannot be used to synthesize 2,2-di-*n*-butylsubstituted systems because the corresponding 2,2-di-*n*-butylsubstituted N-propargyl anilines cannot be synthesized *via* the method described in Chapter 1 (see pages 56-57).

Having synthesized a number of dihydroquinolines, the next step in the reaction sequence was to develop a general procedure for the selective introduction of a chlorine atom into the C3 position of these products.

Chapter 3 - Dihydroquinoline Functionalization

Aromatic rings of aniline-type systems are susceptible to electrophilic attack by halogens,[54] so before any chlorination studies of the dihydroquinoline system could be undertaken, the free dihydroquinolines synthesized in Chapter 2 needed to be N-protected. The N-protecting group chosen was the trifluoroacetamide, due to its ease of preparation and removal. Treatment of a solution of the dihydroquinoline and pyridine in dichloromethane with 1.5 equivalents of trifluoroacetic anhydride provided the N-trifluoroacetyl compounds (75) and (183)-(189) in moderate to excellent yields (Scheme 49).



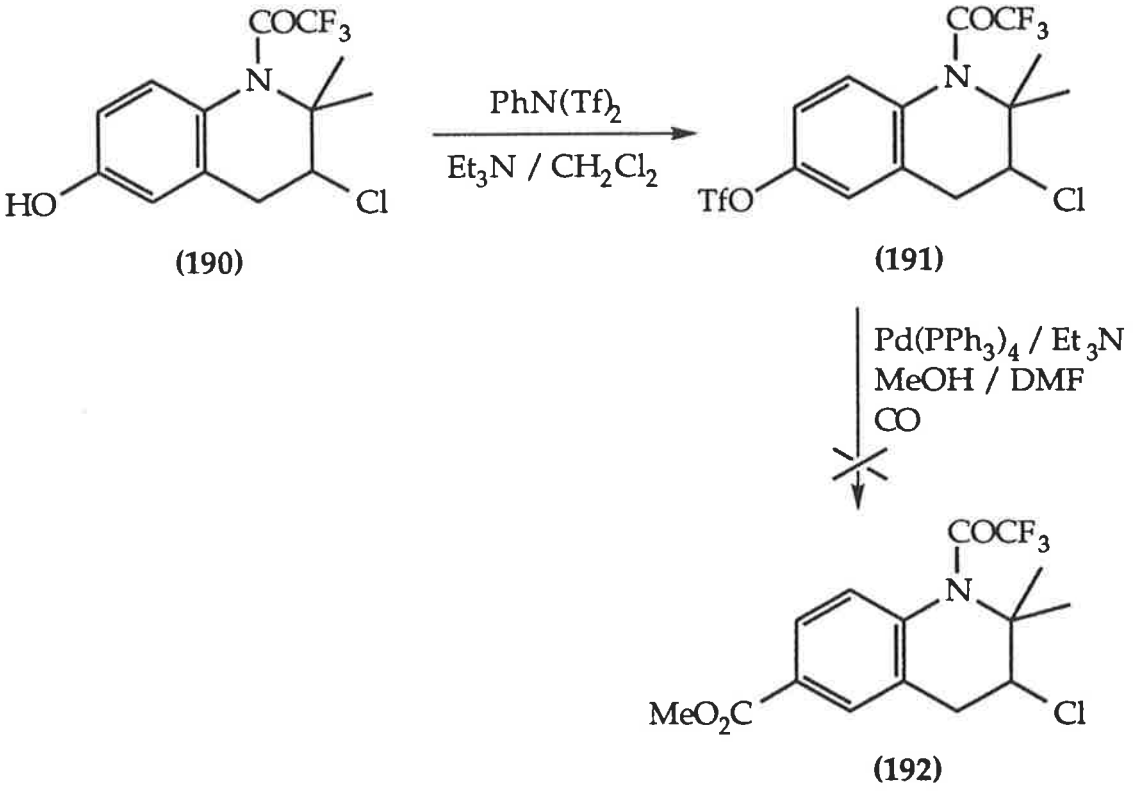
(70) R=Me
(163) R=OMe
(164) R=Br
(171) R=$OSiMe_3$
(167) R=NHAc
(172) R=H
(169) R=CH_2CO_2Et
(170) R=I

(75) R=Me
(183) R=OMe
(184) R=Br
(185) R=OH
(186) R=NHAc
(187) R=H
(188) R=CH_2CO_2Et
(189) R=I

Scheme 49

Previous work in our group[14] has shown that the ester-substituted dihydroquinoline (162) cannot be N-protected due to the delocalization of the lone electron pair on the nitrogen atom by the ester substituent. Attempts to

chlorinate the dihydroquinoline double bond of unprotected (162) resulted in mixtures of polychlorinated compounds that were extremely difficult to separate chromatographically.[55] Since a synthesis of an ester-substituted analogue of virantmycin was still desirable, an alternative route to an N-protected ester-substituted dihydroquinoline was sought.

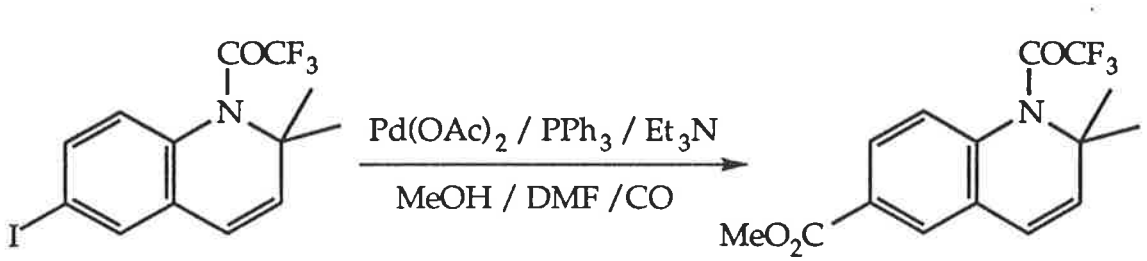


Scheme 50

The first approach was to carry out a palladium-catalyzed insertion of carbon monoxide[56,57] on the triflate (191), which was easily prepared[58] from the hydroxy-substituted compound (190) (Scheme 50). However, attempts to induce carbon monoxide insertion into the carbon-oxygen bond of the triflate (191) using a procedure modified from that of Gerlach and Wollmann[56] were unsuccessful, with starting material regained on workup. Due to the low

reactivity of the triflate moiety towards carbon monoxide insertion, it was decided to use the iodo-substituted (189) in further carbonylation studies due to the greater reactivity of the carbon-iodine bond towards oxidative addition to palladium.[79]

Thus, in a modification of a literature procedure,[57] a mixture of the iodo-substituted dihydroquinoline (189), palladium acetate, triphenylphosphine, triethylamine, methanol and dimethylformamide was stirred at 100° under an atmosphere of carbon monoxide for 4 hours (Scheme 51). Aqueous workup provided the desired ester-substituted dihydroquinoline (193) in a moderate yield. The ^{1}H nmr spectrum of the product (193) exhibited a new signal at δ 3.92, corresponding to the hydrogens of the ester methoxy group, as well as two doublets at δ 5.81 and 6.45 for the two alkene hydrogens on the dihydroquinoline double bond. An infrared spectrum of (193) showed two carbonyl absorptions at 1780 and 1690 cm^{-1} for the ester and amide carbonyl groups respectively. The high wavenumber value for the ester absorption may be due to (193) being a vinylogous imide.

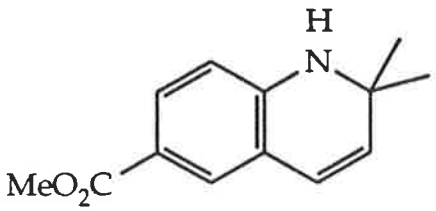


(189) **(193)**

Scheme 51

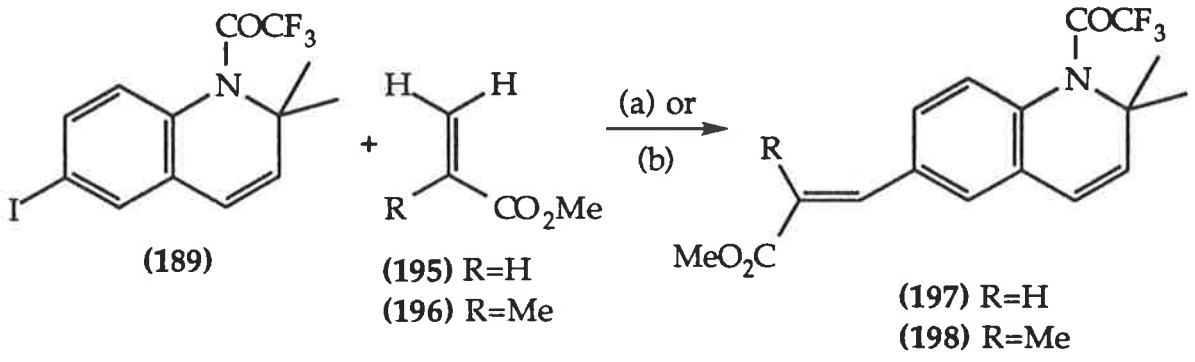
The carbonylation reaction also afforded a small amount of the deprotected compound (194), whose ^{1}H nmr showed a signal at δ 3.83 for the hydrogens of

the ester methyl group and a broad singlet at δ 4.13, corresponding to the NH hydrogen. The infrared spectrum of (194) showed an NH absorption at 3400 cm^{-1} and a single carbonyl absorption at 1705cm^{-1}. The mechanism of formation of (194) is unknown, but possibly involves methanolysis of the trifluorocaetamide facilitated by the triethylamine present in the reaction mixture.



(194)

The reactivity of the iodo-substituted dihydroquinoline system (189) towards Heck conditions[82] was also investigated (Scheme 52).



(189) **(195)** R=H **(196)** R=Me **(197)** R=H **(198)** R=Me

(a) $Pd(OAc)_2/PPh_3/Et_3N/\Delta$
(b) $Pd(PPh_3)_4/PPh_3/Et_3N/DMF/\Delta$

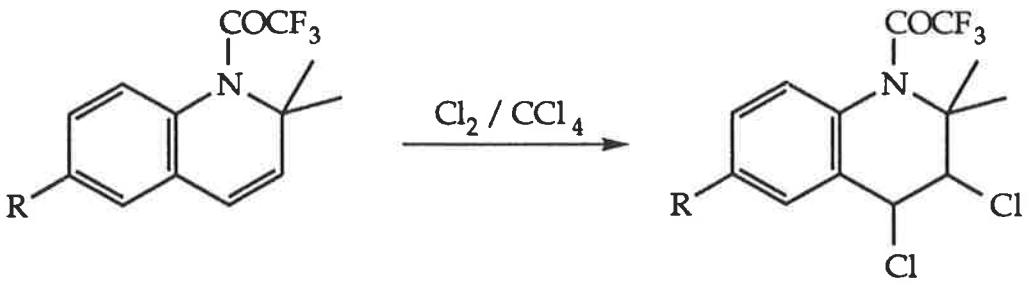
Scheme 52

Initial reactions attempted to couple the iodide (189) with methyl methacrylate (196) to give (198) (Scheme 52, conditions (a)), but no reaction was observed. Even the use of increased amounts of catalyst and/or an elevated reaction temperature gave only the starting iodide (189) on workup.

Further attempts at the Heck reaction were carried out using methyl acrylate (195) as the alkene. Refluxing a mixture of the iodide (189), methyl acrylate, palladium acetate and triphenylphosphine in triethylamine for 4 hours (Scheme 52, conditions (a)) resulted only in the starting materials being regained on workup. Changing the catalyst to palladium *tetrakis*(triphenylphosphine) (0) and using dimethylformamide as the solvent (Scheme 52, conditions (b)) also provided much the same result, with the starting iodide (189) and a trace amount of the unsubstituted dihydroquinoline (187) obtained on workup.

Time constraints prevented further investigation of the Heck reaction as applied to the iodide (189).

Chlorination of the N-trifluoroacetyl dihydroquinolines (183)-(189) and (193) with a 2.4M solution of chlorine in carbon tetrachloride proceeded smoothly to give excellent yields of the 3,4-dichlorotetrahydroquinolines (199)-(206) (Scheme 53).

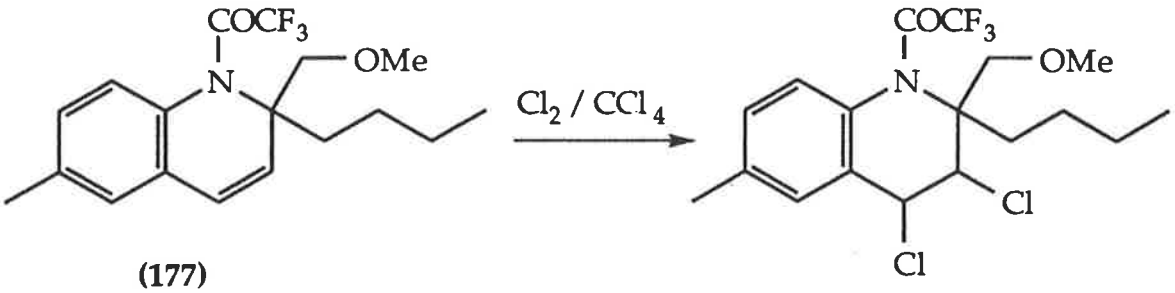


(183) R=OMe
(184) R=Br
(185) R=OH
(186) R=NHAc
(187) R=H
(188) R=CH_2CO_2Et
(189) R=I
(193) R=CO_2Me

(199) R=OMe
(200) R=Br
(201) R=OH
(202) R=NHAc
(203) R=H
(204) R=CH_2CO_2Et
(205) R=I
(206) R=CO_2Me

Scheme 53

The N-trifluoroacetyl dihydroquinoline (177) with the larger side chains was also successfully chlorinated using the above conditions to give a 61% yield of the dichlorotetrahydroquinoline (207) (Scheme 54).



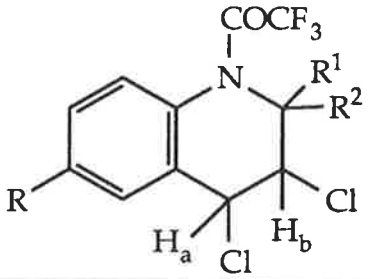
(177)

(207)

Scheme 54

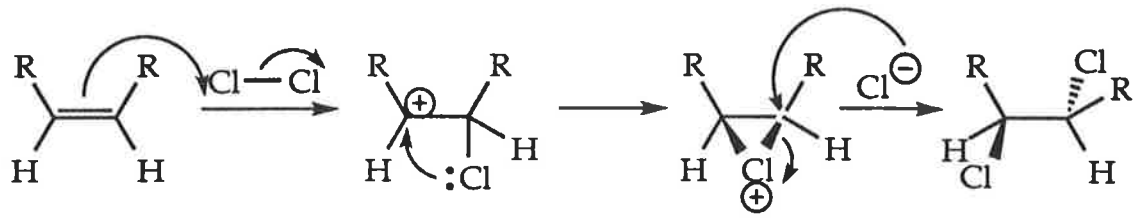
Features common to all of the ^1H nmr spectra of these dichloro compounds were the absence of any signals for olefinic hydrogens and the appearance of two doublets at approximately δ 4.5 and 5.2, corresponding to the two methine hydrogens attached to a chlorine-bearing carbon atom. The coupling constants for these doublets were small, ranging from 4-6 Hz (Table 4), which indicated a dihedral angle of 60°, suggesting *cis* stereochemistry.[58] Further support for the formation of a *cis*-dichloro compound was the fact that the coupling constants for the hydrogens under chlorine atoms were significantly lower than the 9-13 Hz expected in *trans*-coupled systems.[58]

Table 4 - Coupling constants for dichlorotetrahydroquinolines



Compound	R	R^1	R^2	$J(H_a, H_b)$ (Hz)
(200)	OMe	Me	Me	4.5
(201)	Br	Me	Me	4.4
(202)	OH	Me	Me	4.6
(203)	NHAc	Me	Me	4.4
(204)	H	Me	Me	4.5
(205)	CH_2CO_2Et	Me	Me	4.5
(206)	I	Me	Me	4.4
(207)	CO_2Me	Me	Me	4.3
(208)	Me	CH_2OMe	*n*-Bu	6.2

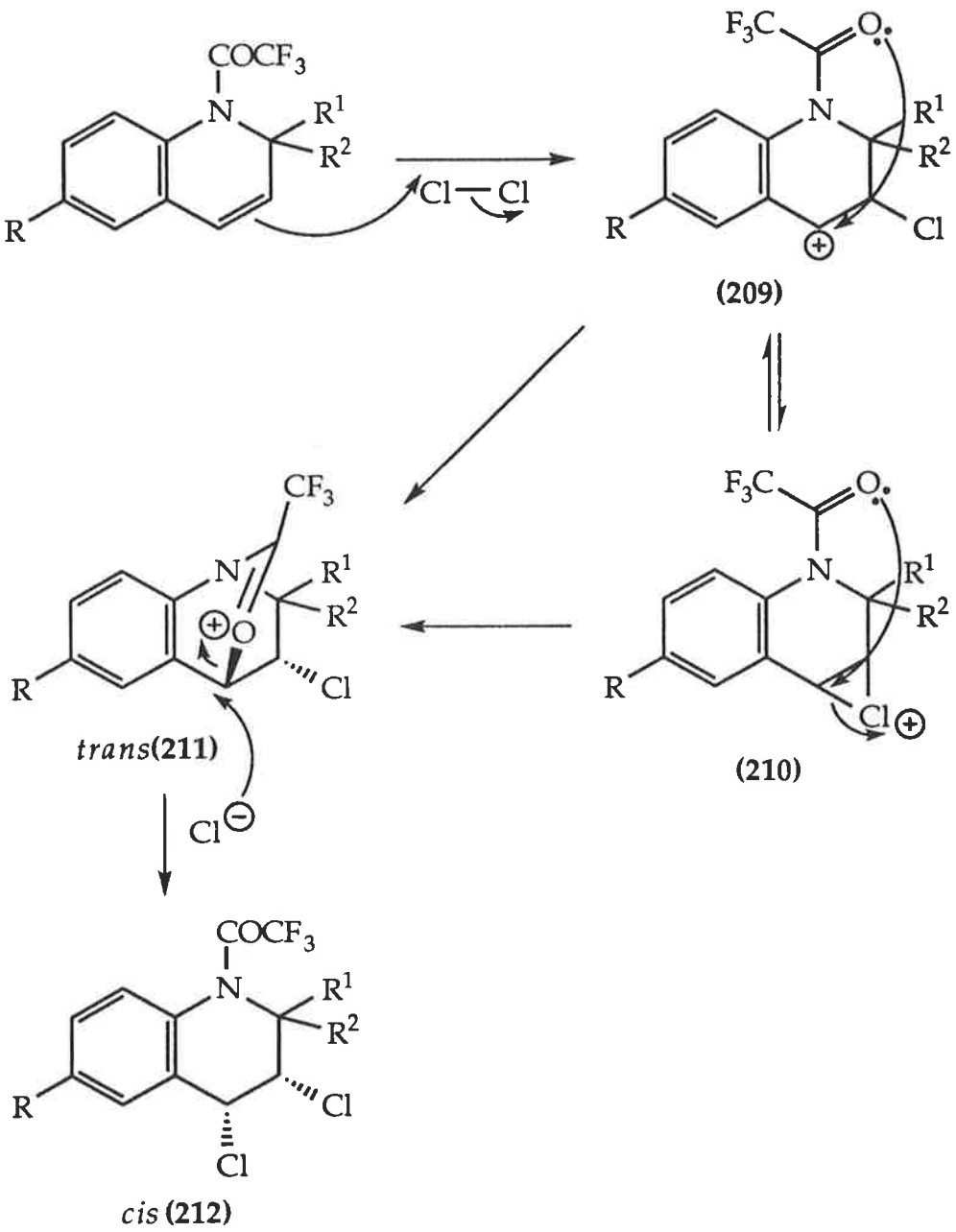
Addition of molecular chlorine to double bonds usually proceeds *via* a chloronium ion[54] (208), which is then ring-opened by chloride ion attack from the opposite face to give a *trans*-dichloro compound (Scheme 55).



(208)

Scheme 55

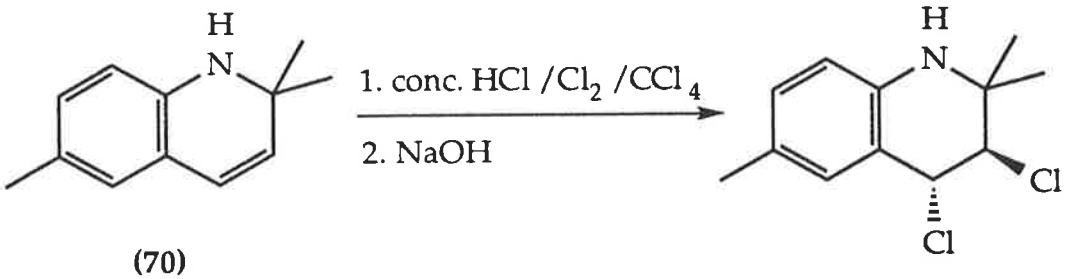
However, the apparent *cis* geometry of the dichlorotetrahydroquinolines (199)-(207) indicates a more complicated mechanism than that shown in Scheme 55. The unexpected *cis*-addition of chlorine to a dihydroquinoline double bond has been observed previously in our group[14] and was rationalized by the possible participation of the N-protecting group (Scheme 56). The benzylic carbocation (209) may be trapped by the carbonyl oxygen of the acyl group, giving the *trans*-intermediate (211), which is then attacked by chloride ion to give the *cis*-product. Alternatively, the chloronium ion (210) may be attacked by the carbonyl oxygen atom at the benzylic position, which also results in the formation of the *trans*-intermediate (211).



Scheme 56

The large range of N-acyl dihydroquinolines in this study that underwent *cis*-addition of chlorine to the double bond shows that the initial observation[14] was not an isolated incident.

Support for this protecting-group participation theory was provided by studies of the chlorination of the unprotected dihydroquinoline (70) (Scheme 57). Treatment of the hydrochloride salt of (70) with a solution of chlorine in carbon tetrachloride produced, after neutralization and purification, the dichloro compound (213) in a 47% yield. The ^1H nmr spectrum of (213) exhibited the two doublets expected for the hydrogen atoms under chlorine at δ 3.98 and 4.76, with a coupling constant of 9.2 Hz. This significant increase in the magnitude of the coupling constant compared to the N-protected dichloro compounds indicates a *trans-* structure for (213) and suggests that in the absence of an N-acyl protecting group, the chlorination proceeds *via* the expected chloronium ion mechanism.

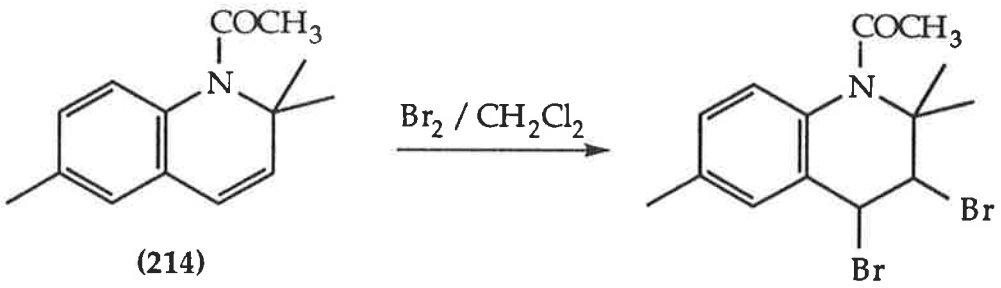


(70) (213)

Scheme 57

Having made an extensive study of the chlorination of N-acyl dihydroquinolines, it was of interest to see if another halogen, for example bromine, reacted towards them in the same manner. Thus, a solution of the N-acetyl dihydroquinoline (214) (available from previous work[14] in our group) in dichloromethane was treated with one equivalent of bromine (Scheme 58) to give the dibromo compound (215) in a 91% yield. The product dibromo tetrahydroquinoline (215) was unstable, but was long-enough lived

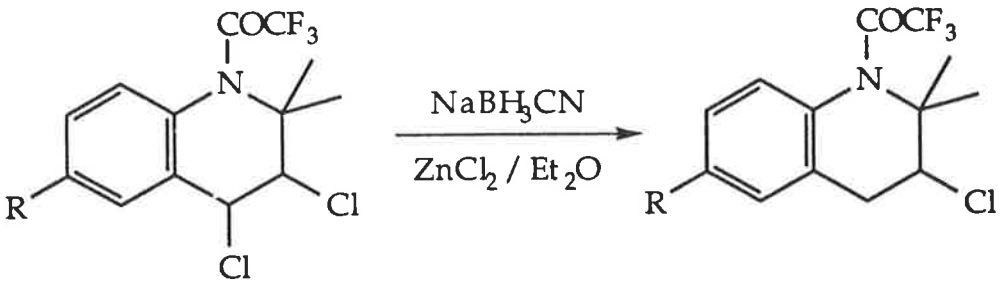
for spectroscopic study. The ^1H nmr spectrum of (215) showed two doublets at δ 4.89 and 5.55, corresponding to the hydrogens attached to the bromine-bearing carbon atoms. The coupling constant of 3.9 Hz for these doublets suggested that *cis*-addition of bromine had occurred and that the mechanism of its addition may be similar to that of the addition of chlorine to N-acyl dihydroquinolines.



(214) (215)

Scheme 58

The selective removal of the benzylic chlorine atom of the dichloro-tetrahydroquinolines was then investigated using a literature procedure[22] that has been applied to these systems by our group in earlier work.[10,14] Treatment of a solution of the dichloro compounds in ether with zinc-modified cyanoborohydride[22] gave the corresponding 3-chlorotetrahydro-quinolines in moderate to excellent yields (Scheme 59). 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.

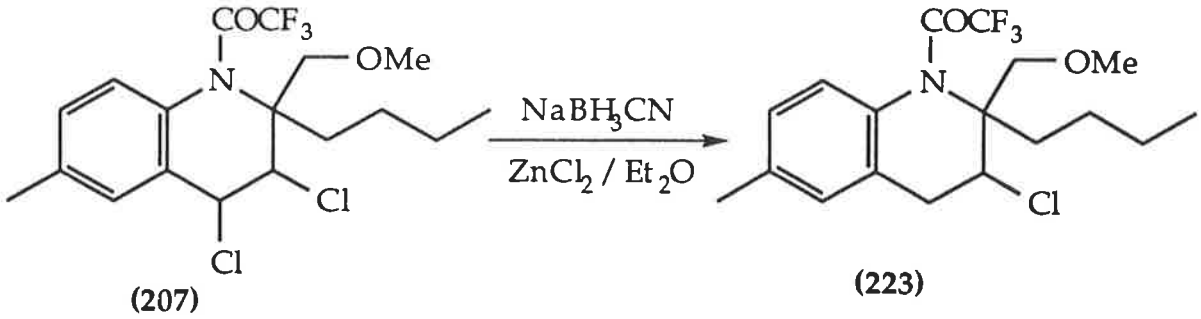


(199) R=OMe
(200) R=Br
(201) R=OH
(202) R=NHAc
(203) R=H
(204) R=CH_2CO_2Et
(205) R=I
(206) R=CO_2Me

(216) R=OMe
(217) R=Br
(190) R=OH
(218) R=NHAc
(219) R=H
(220) R=CH_2CO_2Et
(221) R=I
(222) R=CO_2Me

Scheme 59

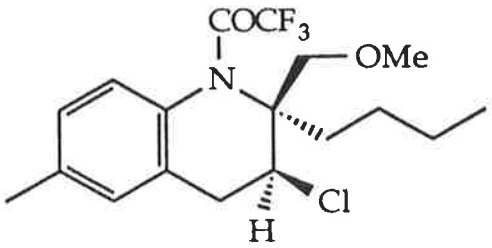
The distinctive ABX splitting pattern of the hydrogens on the heterocyclic ring observed in the ^1H nmr spectra of the 3-chloro compounds allowed their positive identification. Two doublet of doublets were observed in the region δ 3.0-3.2, both with a large geminal coupling constant (15-16 Hz) and a smaller vicinal coupling constant (3-6 Hz), and were assigned to the two diastereotopic hydrogens of the benzylic methylene group. A third doublet of doublets, assigned to the hydrogen attached to the chlorine-bearing carbon atom, was observed further downfield at approximately δ 4.2, with two small vicinal coupling constants due to coupling with the hydrogens of the adjacent methylene group.



(207) (223)

Scheme 60

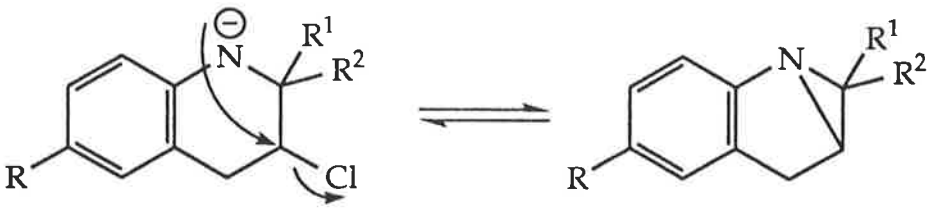
The dichlorotetrahydroquinoline with the larger side chains (207) was also selectively dechlorinated to give an excellent yield of the corresponding monochloride (223) (Scheme 60). The ^{1}H nmr spectrum of the product (223) showed the three sets of doublet of doublets expected for the 3-chloro system at δ 3.06 (J 4.3, 16.0 Hz), 3.53 (J 7.2, 16.0 Hz) and 4.28 (J 4.3, 7.2 Hz). Nuclear Overhauser enhancement (n.O.e.) experiments were conducted to determine the stereochemistry of the chlorine atom with respect to the side chains α- to the nitrogen atom. Irradiation at δ 4.28 resulted in enhancement of the adjacent benzylic methylene group only. Irradiation of one of the doublets of the OCH_2 AB quartet at δ 3.9 gave enhancement of the corresponding doublet only. However, irradiation at δ 1.9 (the methylene group closest to the nitrogen atom in the butyl chain) gave a 1.7% enhancement of the OCH_2 AB quartet and a 1.4% enhancement of the hydrogen attached to the chlorine-bearing carbon atom. The latter enhancement suggests that the *n*-butyl group and the methine hydrogen atom are in a *cis* arrangement on the heterocyclic ring, which in turn suggests (223a) as a probable structure for the monochloro compound.



(223a)

It is possible that the stereoselectivity observed in (223) was introduced during addition of molecular chlorine to the dihydroquinoline (177). To give the stereochemistry suggested by the n. O. e. experiments carried out on (223), the initial addition of a δ^+ chlorine atom must come from the same face as the methoxymethyl group. This approach might be facilitated by an electronic interaction, with the δ^- oxygen atom of the methoxymethyl group acting to stabilize any δ^+ sites in the transition state. Since the stereochemistry of the chlorine atom in the 3-position is, presumably, left untouched during the selective dechlorination step, the stereochemistry introduced at that centre in the chlorination of (177) should be carried through to the monochloro compound (223).

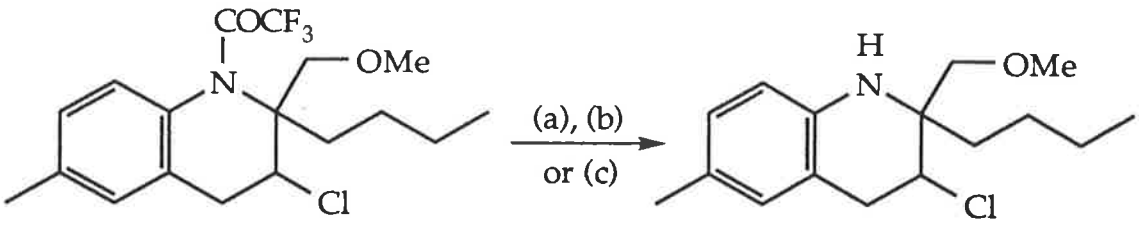
The final step in the sequence to give a virantmycin analogue was deprotection of the nitrogen atom. Trifluoroacetamides are usually hydrolyzed relatively easily under basic conditions,[8,9,27] but this type of hydrolysis could pose a problem with the 3-chloro systems, since the basic conditions may facilitate elimination and/or the anion on nitrogen formed under these conditions could displace chloride to form an aziridine system with the general structure of (224) (Scheme 61). Aziridine formation such as that shown in Scheme 61 has been observed for similar systems,[2,4,8] and attempts to selectively ring open the aziridine system resulted in mixtures of tetrahydroquinolines and unwanted dihydroindoles.[8]



(224)

Scheme 61

Therefore, initial attempts to hydrolyze the trifluoroacetamide moiety of the 3-chloro compounds focussed on the use of acid catalysis (Scheme 62, conditions (a)). However, refluxing a solution of (223) in ethanol in the presence of a catalytic amount of sulphuric acid resulted only in the recovery of the starting material after a 48 hour reaction time.



(223) (225)

(a) H_2SO_4 (cat.) / EtOH / H_2O
(b) 10% KOH in MeOH / Δ
(c) 10% KOH in MeOH / RT

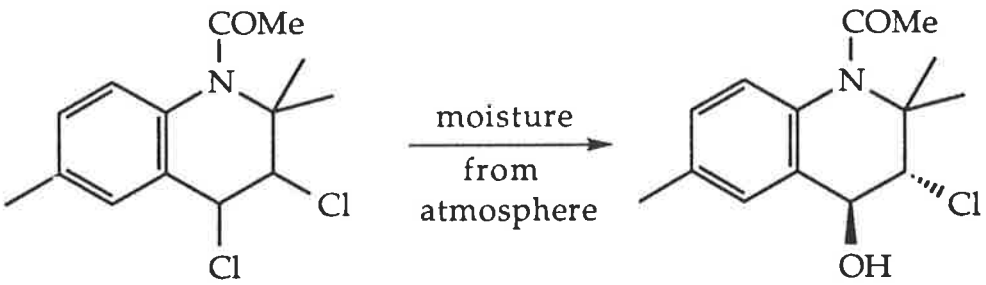
Scheme 62

Since acid-catalyzed hydrolysis was unsuccessful, a base catalyzed reaction was attempted to see if any hydrolysis could be achieved. Treatment of the trifluoroacetamide (223) with a 10% solution of potassium hydroxide in

methanol[8,9] at reflux (Scheme 62, conditions (b)) gave an extremely complex mixture, containing at least five new products by tlc analysis.

However, stirring the trifluoroacetamide (223) in a 10% solution of potassium hydroxide in methanol at room temperature for 2.5 hours (Scheme 62, conditions (c)) provided the parent amine (225) in 75% yield, suggesting that the reflux conditions used above were too harsh. The ^1H nmr spectrum of the free amine (225) showed a singlet at δ 3.35, assigned to the methoxy group hydrogens, a doublet of doublets at δ 4.32, assigned to the hydrogen attached to the chlorine-bearing carbon atom, and a broad singlet at δ 3.90 attributed to the NH group. An IR spectrum of the amine (225) showed an NH absorbance at 3400 cm^{-1} and lacked a carbonyl signal, confirming successful hydrolysis of the trifluoroacetamide.

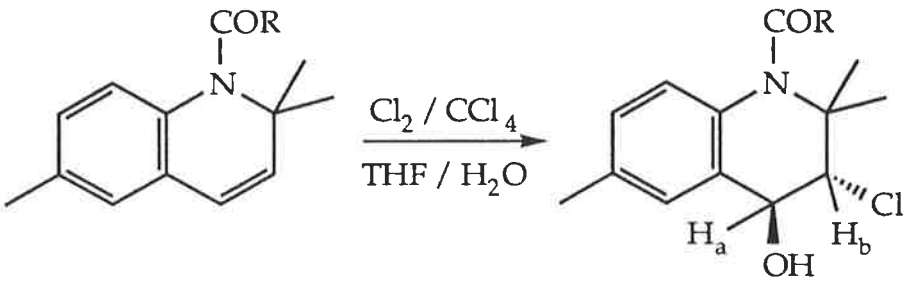
It was also of interest to investigate other possible reactions of the dihydroquinoline double bond. The chlorohydrin (227) was observed[80] as a decomposition product of the dichloro compound (226) (Scheme 63), so the first investigation involved attempting the synthesis of chlorohydrin systems directly from the corresponding dihydroquinolines.



(226) **(227)**

Scheme 63

Initial attempts to synthesize the chlorohydrin system using equimolar amounts of chlorine and water as well as two- and threefold molar excesses of water in tetrahydrofuran produced only low yields of the desired chlorohydrin. Greater success was achieved by using a 1:1 tetrahydrofuran/water mixture with the chlorine solution; the latter method gave the chlorohydrin (227) from the dihydroquinoline[14] (214) (available from previous work) in a 96% yield after a 24 hour reaction time (Scheme 64, R=Me).

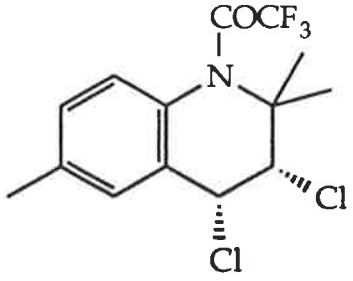


(214) R=Me
(75) R=CF_3

(227) R=Me
(228) R=CF_3

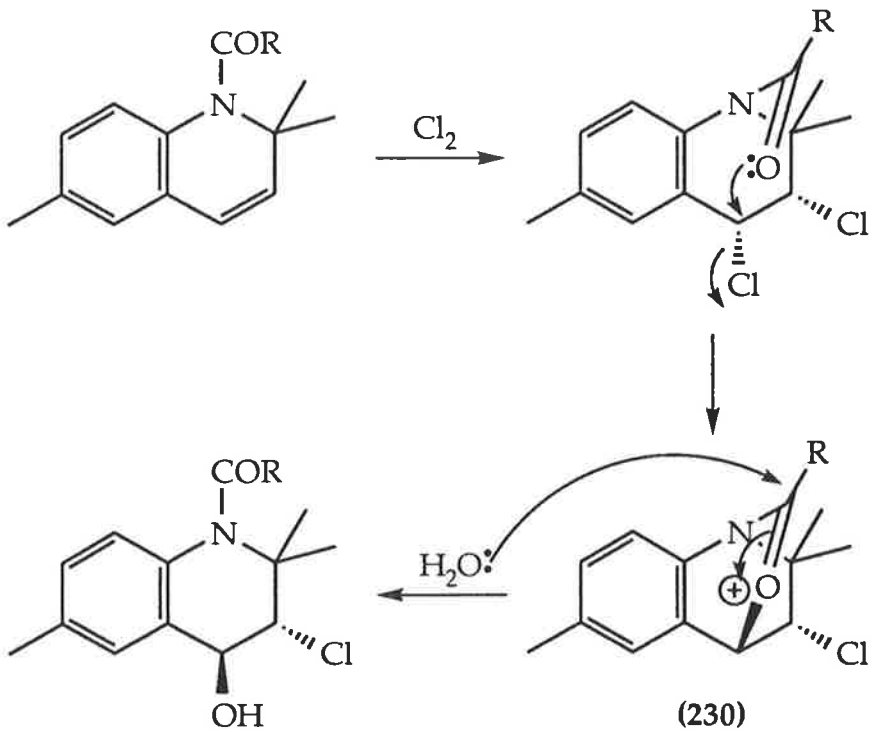
Scheme 64

The N-trifluoroacetyl dihydroquinoline (75) was also subjected to the above conditions, but gave only a 36% yield of the corresponding chlorohydrin (228) after an extended reaction time of 72 hours (Scheme 64, R=CF_3). Also isolated from the same reaction was the *cis*-3,4-dichloro compound (229) in a 47% yield.



(229)

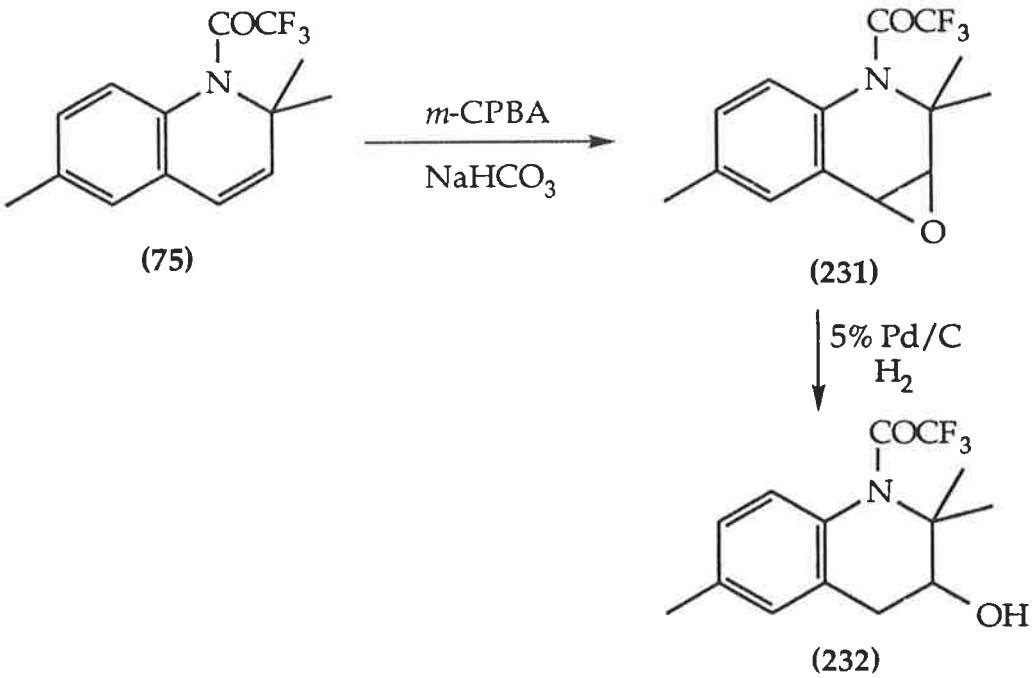
The chlorohydrins (227) and (228) were assigned *trans-* stereochemistry on the basis of the large coupling constants (*ca* 9.5 Hz) observed between H_a and H_b. This stereochemical assignment was confirmed when an X-ray crystal structure[14] of (227) revealed the *trans-* arrangement and the expected regiochemistry of the hydroxy group and the chlorine atom. The noticeable decrease in reaction rate in going from an N-acetyl to an N-trifluoroacetyl derivative supports a reaction mechanism similar to the one proposed in Scheme 56. The products obtained from the reaction of the N-trifluoroacetyl dihydroquinoline (75) indicate that chlorohydrin formation is most likely to proceed *via* an initial, rapid addition of chlorine to the dihydroquinoline double bond followed by conversion to the chlorohydrin as the rate-determining step. A possible mechanism is outlined in Scheme 65.



Scheme 65

Formation of the *cis*-3,4-dichloro system has been discussed previously in this Chapter (see Scheme 56, page 77). Attack of the carbonyl oxygen atom at the benzylic position of the dichloro compound would give the *trans*-intermediate (230), which can then be opened by attack of water at the carbonyl carbon to give the *trans*-chlorohydrin. Nucleophilic attack by the oxygen atom of the acetyl group would be expected to be relatively easy compared to the corresponding process involving the trifluoroacetyl group, which would be made more difficult by the electron withdrawing nature of the trifluoromethyl moiety reducing the nucleophilicity of the oxygen. The above proposed mechanism is supported by the fact that a decrease in reaction rate to form the chlorohydrins is observed in going from an N-acetyl to an N-trifluoroacetyl derivative.

Epoxidation[4] of the double bond of (75) was achieved using *meta*-chloroperoxybenzoic acid and sodium bicarbonate in dichloromethane (Scheme 66). The product epoxide (231), obtained in a 74% yield, showed two doublets in its ^{1}H nmr spectrum at δ 3.41 and 3.86, attributed to the hydrogens of the two epoxide methine groups. The small coupling constant of 4.2 Hz observed for these doublets confirmed the expected *cis*-stereochemistry. Hydrogenolysis of the epoxide (231), using a modification of a reported procedure,[4] provided the alcohol (232) in good yield. The ^{1}H nmr spectrum of (232) resembled that of the related 3-chloro system (77), showing a multiplet at δ 3.89 assigned to the hydrogen on the hydroxyl-bearing carbon and two doublet of doublets at δ 2.82 and 2.94, attributed to the diastereotopic hydrogens of the benzylic methylene group. A number of investigations into the reactions of this alcohol were then undertaken.

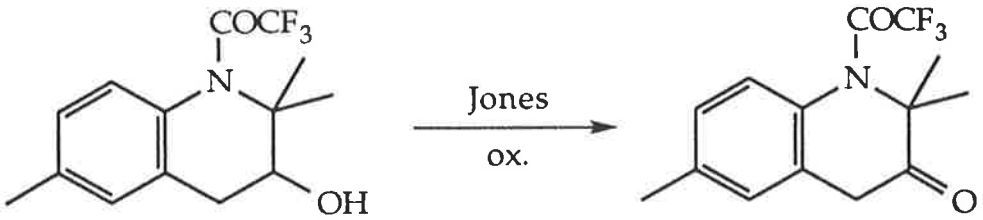


(75) (231) (232)

Scheme 66

Oxidation of the alcohol (232) to the ketone (233) proceeded smoothly using Jones reagent (Scheme 67). However, ^{1}H nmr of the product ketone (233) 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. This led to the conclusion 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. A variable temperature nmr experiment was carried out (see Appendix, page 190), which enabled complete interpretation of the ^{1}H nmr spectrum of (233). Heating the 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 dramatically. The hydrogens of the two geminal dimethyl groups appeared as two sharp singlets at δ 1.34 and 1.70, while well-defined doublets at δ 3.36 and 3.87 were attributed to the diastereotopic hydrogens of the benzylic methylene group.

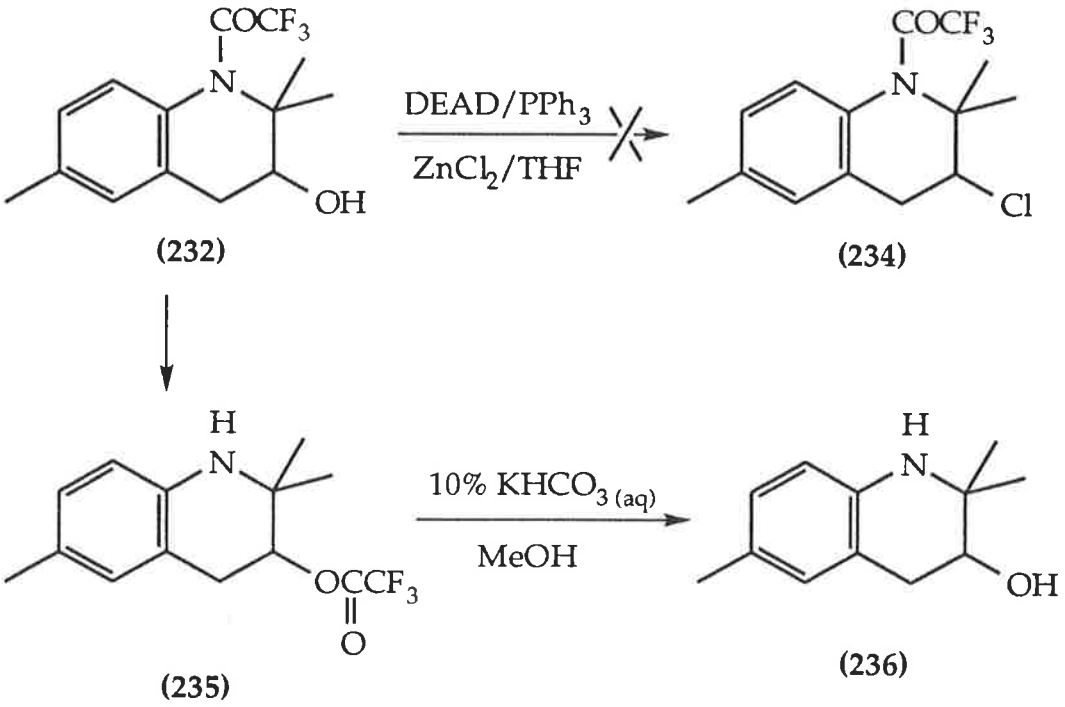


(232) (233)

Scheme 67

The alcohol (232) was subjected to Mitsunobu[76, 77] conditions in attempts to introduce a halogen atom into the 3-position. However, using a reported procedure,[78] in which zinc chloride was used as the halide source (Scheme 68), the sole product isolated was not the expected 3-chloro derivative (234) but the trifluoroacetate (235), formed *via* acetyl group transfer from the nitrogen atom to the oxygen atom. The ^{1}H nmr spectrum of the trifluoroacetate (235) showed a broad NH signal at δ 3.56 and three doublet of doublets at δ 5.10, 2.86 and 3.15, assigned to the hydrogen on the oxygen-bearing carbon atom and the two hydrogens of the benzylic methylene group respectively. An infrared spectrum of the trifluoroacetate (235) showed both NH and carbonyl signals at 3400 and 1780 cm^{-1} respectively, with the higher frequency of the carbonyl signal (compared to the usual position of the amide carbonyl signal at *ca* 1700 cm^{-1}) confirming the presence of a trifluoroacetate. Other attempts at the same reaction using different halide sources such as

tetrabutylammonium bromide and tetrabutylammonium chloride also resulted in the formation of the trifluoroacetate (235).

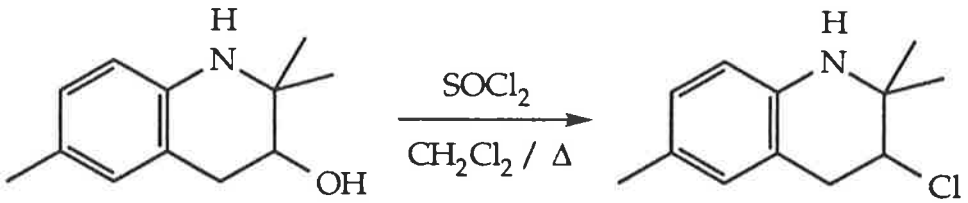


Scheme 68

Tlc and ^1H nmr of a sample of the alcohol (232) 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. Mitsunobu conditions seem to facilitate the conversion, however, since approximately equal amounts of the alcohol and the trifluoroacetate (235) were detected in the old sample of the alcohol (232).

Hydrolysis of the trifluoroacetate (235) using 10% aqueous potassium carbonate in methanol provided the aminoalcohol (236) (Scheme 68). Systems related to (236) have been converted to the corresponding 3-chloro compounds using thionyl chloride,[4] but application of this procedure to the aminoalcohol (236) (Scheme 69) gave only an intractable product mixture as

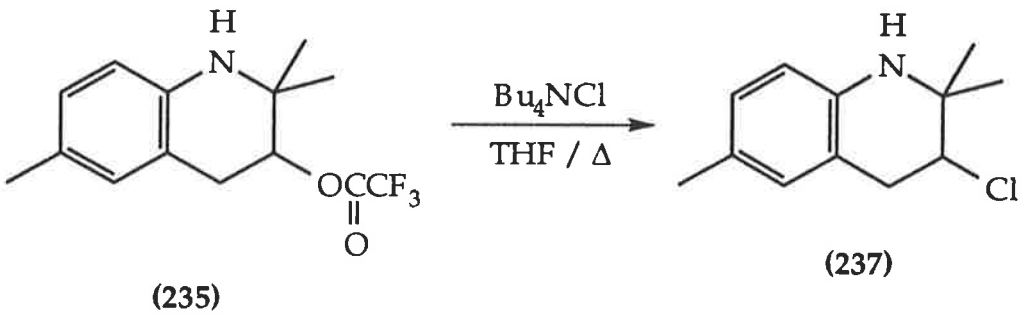
evidenced by tlc and ^1H nmr in which the expected signals for the chloro compound (237) could not be detected.



(236) (237)

Scheme 69

Direct S_N2 displacement of the trifluoroacetyl moiety of (235) with chloride ion (using tetrabutylammonium chloride as the chloride source) (Scheme 70) met with more success; however, the reaction was very slow and the product 3-chloro compound (237) was unable to be separated from the starting trifluoroacetate (235). Evidence for the presence of the chloro compound (237) was seen in the ^1H 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 (235) and the monochloride (237) respectively. A mass spectrum of the mixture showed molecular ions for both the trifluoroacetate (235) (m/z 287) and the chloro compound (237) (m/z 209/211).



(235) (237)

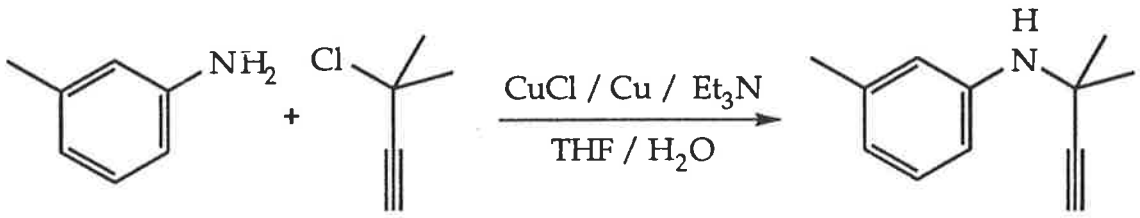
Scheme 70

The work detailed in this chapter has shown that the dihydroquinoline system, once suitably protected as an amide, may be converted to a number of substituted tetrahydroquinoline derivatives, after which the amide may be hydrolyzed to give the parent amine.

Chapter 4 - Miscellaneous Coupling and Cyclization Reactions

Previous work on the coupling[10-13] and the cyclization[14, 80] reactions within our group has concentrated entirely on *para*-substituted anilines and their N-propargyl derivatives. N-propargyl anilines with *para*-aromatic substituents produce only one product on cyclization due to the symmetrically substituted aromatic moiety, so it was of interest to investigate the behaviour of *ortho*- and *meta*-substituted compounds towards the coupling and, more specifically, the cyclization reactions.

The study began with the reaction of *m*-toluidine (238) with the chloroalkyne (61), which produced the corresponding N-propargyl aniline (239) in 83% yield (Scheme 71). A ^{1}H nmr spectrum of the product exhibited singlets at δ 1.60, 2.29 and 2.36 which were attributed to the hydrogens of the equivalent geminal dimethyl groups, the aryl methyl group and the acetylenic hydrogen respectively, confirming the introduction of the propargyl moiety.

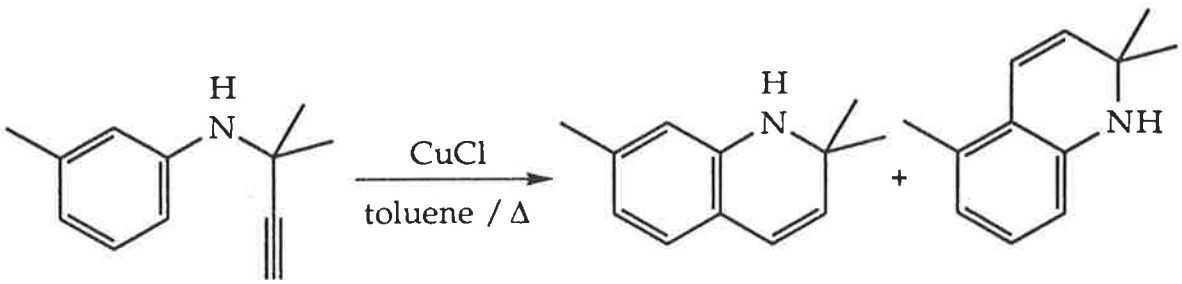


(238) **(61)** **(239)**

Scheme 71

Cyclization[14] of the N-substituted aniline (239) proceeded smoothly using cuprous chloride in refluxing toluene (Scheme 72) to give a 1:1 mixture of the

dihydroquinolines (240) and (241), which were inseparable by chromatography. The ^1H nmr spectrum of the dihydroquinoline mixture showed four doublets in the alkene region; two for each dihydroquinoline structure. The recovery of a 1:1 mixture of dihydroquinoline products from the cyclization of (239) indicates that cyclization onto each position *ortho*- to the nitrogen atom is equally favoured.

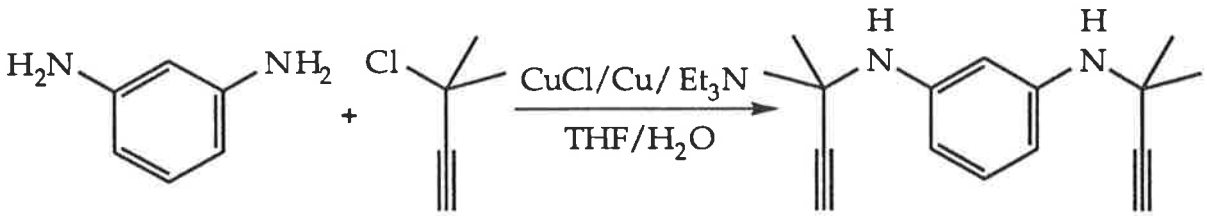


(239) (240) (241)

Scheme 72

Another *meta*-substituted system studied was the diamine (242), which was of interest for comparison purposes. The *para*-substituted diamine (133) was studied in Chapters 1 and 2, and was found to be unstable due to oxidation to the iminoquinone system (see pages 48-49 and 63), and it was hoped that the *meta*- orientation of the amino groups of (242) would reduce the likelihood of oxidation, making derivatives of (242) more stable than their *para*-counterparts. Reaction of the diamine (242) with 2.5 equivalents of the chloroalkyne (Scheme 73) gave the *bis*-N-propargyl compound (243) in a 31% yield. The moderate yield was attributed to problems encountered due to formation of a copper complex with the diamine system. The product dialkyne (243) showed resonances in its ^1H nmr spectrum at δ 1.61 and 2.36,

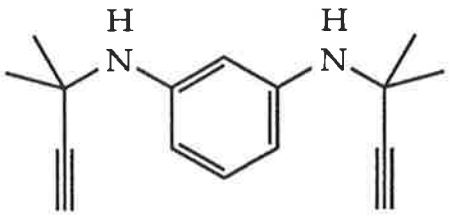
assigned to the hydrogens of the four equivalent methyl groups and the two acetylenic hydrogens respectively.



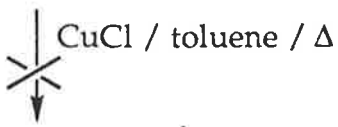
(242) **(61)** **(243)**

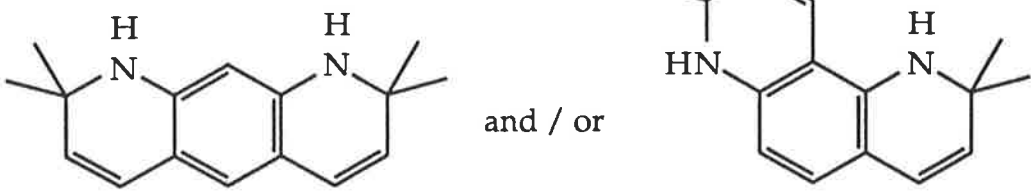
Scheme 73

The dialkyne (243) was not as stable as anticipated, and subjection of it to the cyclization conditions[14] (Scheme 74) resulted in the formation of an intractable mixture whose ^1H nmr did not exhibit any signals that could be attributed to compounds such as (244) and (245).



(243)

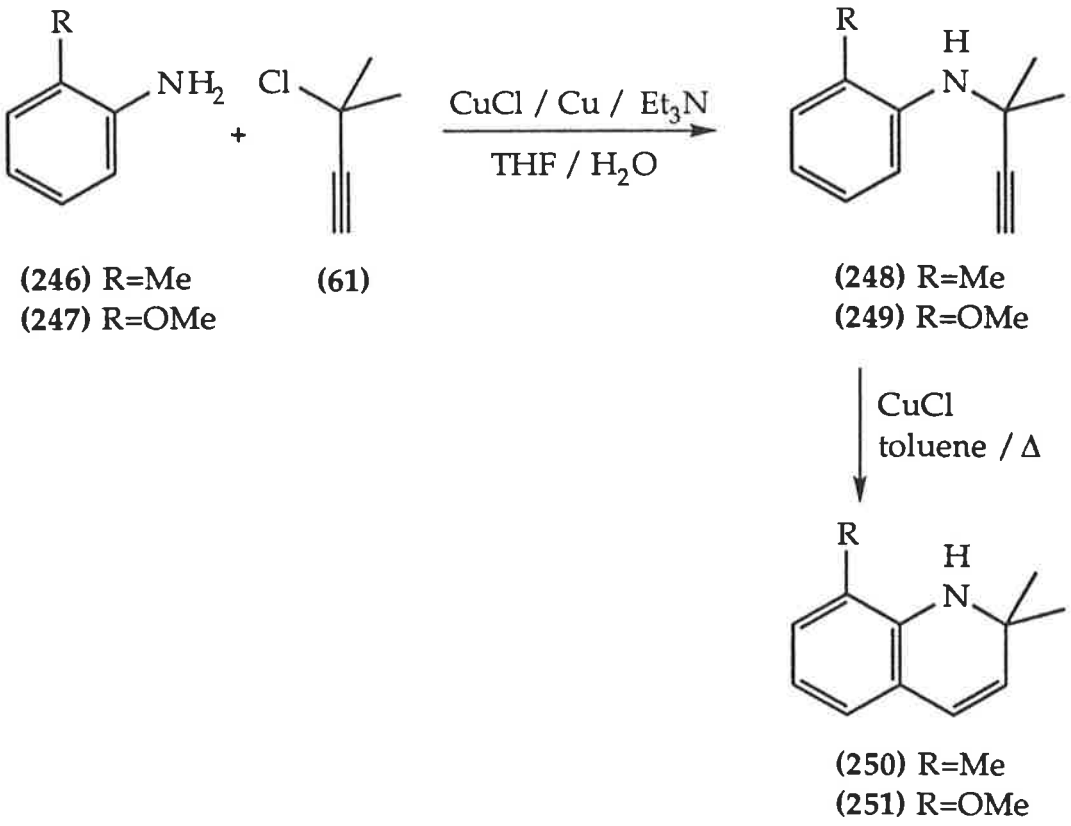




(244) **(245)**

Scheme 74

A study of the coupling and cyclization reactions on *ortho*-substituted systems was also undertaken. The *ortho*-substituted compounds were of interest because their reactivity towards both the coupling and cyclization reactions would give information on the effect of having a substituent adjacent to the nitrogen atom. Reaction of *o*-toluidine (246) and *o*-anisidine (247) with the chloroalkyne (61) gave the N-propargyl anilines (248) and (249) respectively in moderate yield (Scheme 75). Cyclization[14] of these N-propargyl anilines (Scheme 75) to the dihydroquinolines (250) and (251) proceeded at a much slower rate when compared to the corresponding *para*-substituted analogues (72) and (76). The *ortho*-substituted systems both required a reaction time of 1.5 hours for complete cyclization, while the reaction times for the *para*-substituted systems (72) and (76) were 1 hour and 20 minutes respectively. The explanation for the increase in the reaction time of the *ortho*-substituted compounds may be twofold: the steric bulk introduced by the substituent being so close to the nitrogen atom would hinder the cyclization, since easy access to the nitrogen atom is an important part of the mechanism (see page 26). The decreased reaction rate may also be due to statistical factors: the *ortho*-substituted system has only one possible site upon which to cyclize, whereas the *meta*- and *para*-substituted compounds possess two such sites. Therefore, the *ortho*-substituted system is 50% less likely to be in the right conformation for cyclization than the *meta*- and *para*-substituted compounds, which would result in the observed decrease in reaction rate.



(246) R=Me
(247) R=OMe

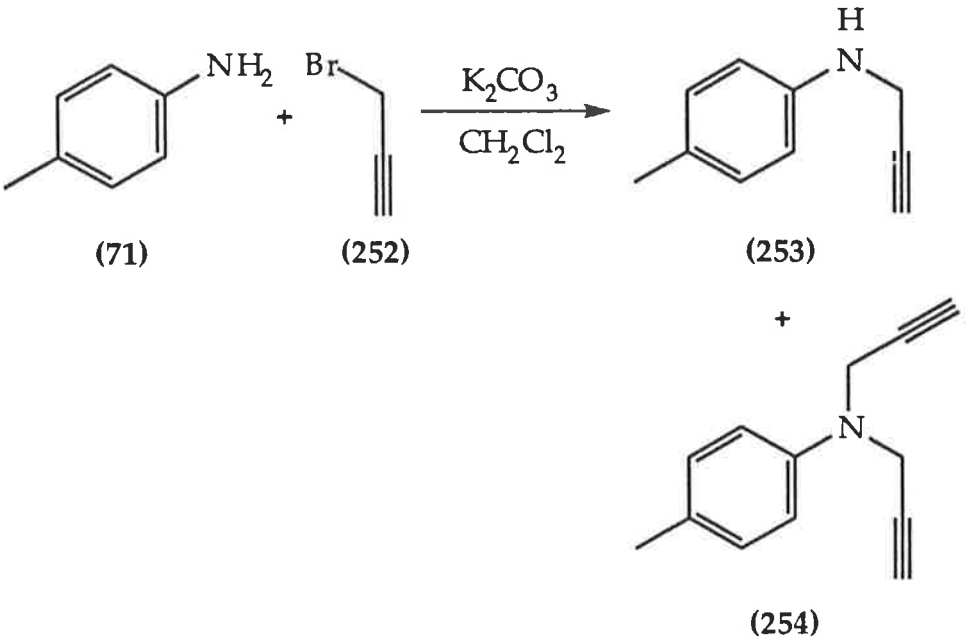
(61)

(248) R=Me
(249) R=OMe

(250) R=Me
(251) R=OMe

Scheme 75

Another area of interest was the study of the cyclization of N-propargyl anilines with either one or no substituents α- to the nitrogen atom. It would be expected that once systems such as the latter have cyclized to a dihydroquinoline, rapid oxidation to the fully aromatic quinoline should follow. This process has not been observed for the 2,2-dimethyl substituted dihydroquinolines synthesized in Chapter 2 since aromatization to the quinoline would involve an energetically unfavourable loss of methane.

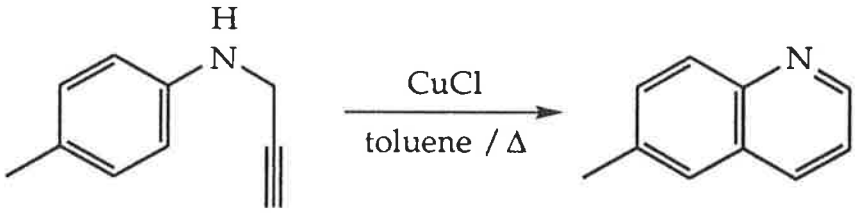


(71) (252) (253) (254)

Scheme 76

The first system of this type studied was the N-propargyl aniline (253), synthesized from the reaction of *p*-toluidine and propargyl bromide (252) (Scheme 76). ^{1}H nmr of the N-substituted aniline (253) exhibited a singlet resonance for the hydrogens of the aryl methyl group at δ 2.25 as well as a resonance for the acetylenic hydrogen at δ 2.20, which was split into a triplet (J 2.4 Hz) by long range coupling to the hydrogens of the methylene group attached to the nitrogen atom. Also present in the ^{1}H nmr spectrum of (253) was a broad singlet at δ 3.74 that exchanged with D_2O, indicating the presence of an NH group, which was confirmed with an absorbance at 3405 cm^{-1} in the infrared spectrum of (253). The dialkyne (254) was also obtained from the same reaction, and showed similar spectral properties to that of (253), but lacked NH signals in both ^{1}H nmr and infrared spectra.

The cyclization procedure for (253) needed to be modified, since it was found that as soon as any quinoline was produced, it formed a complex with the copper present, thus removing the copper from the catalytic cycle. Therefore, the cyclization of (253) was carried out using one molar equivalent of cuprous chloride in refluxing toluene (Scheme 77). Modification of the workup after cyclization was also required, since the resulting copper-quinoline complex needed to be broken up. This was achieved by acid extraction of the reaction mixture, addition of ethylenediaminetetraacetic acid to the acid extracts, followed by basification and extraction with dichloromethane. This method gave 6-methylquinoline (255), whose spectral data was consistent with that reported.[66]

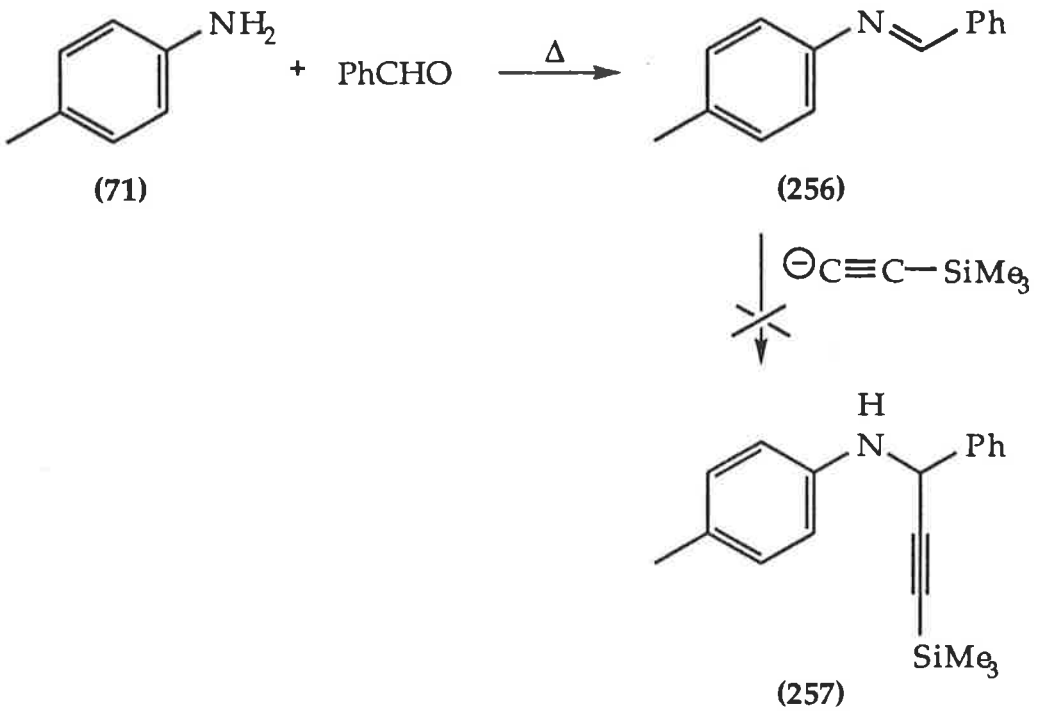


(253) (255)

Scheme 77

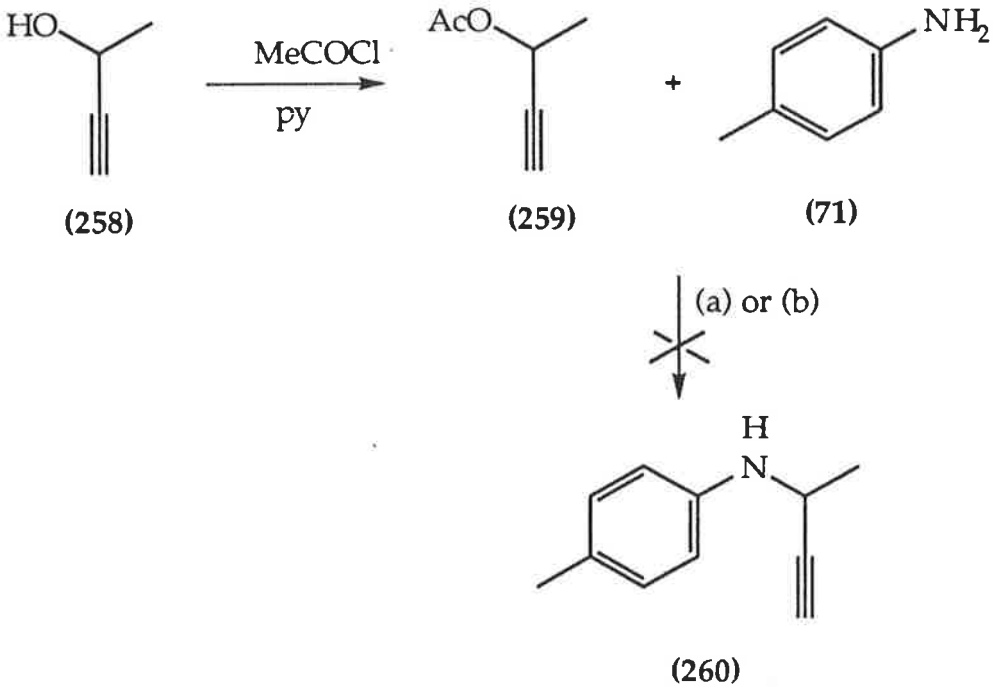
Initial attempts to synthesize an N-propargyl aniline with one substituent α- to the nitrogen atom concentrated on the reaction of the imine[67] (256) with an appropriate acetylide anion (Scheme 78). However, attempts to add the trimethylsilylacetylide anion to the carbon-nitrogen bond of the imine (256) were unsuccessful, and a reference[68] was found that stated that Grignard reagents and related nucleophiles do not add to imines unless the nitrogen atom is quaternized. A reaction of the latter type would give an N,N-*bis*-alkylated compound, which have been shown to be unreactive towards

cyclization (see Chapter 2, page 63). Therefore, an alternative route to the desired N-propargyl system was sought.



Scheme 78

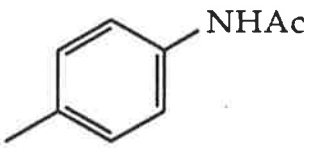
Imada *et al*[20] reported that the amination of propargyl acetates proceeds readily under copper catalysis, so this method was adopted to synthesize the N-propargyl aniline (260) (Scheme 79, conditions (a)).



(a) $CuCl/Et_3N/THF/\Delta$
(b) K_2CO_3/THF

Scheme 79

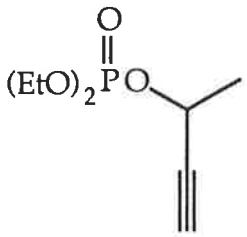
The acetate (259) required for the coupling reaction was prepared in excellent yield by reacting the corresponding alcohol with acetyl chloride (Scheme 79). However, attempts to couple the acetate (259) with *p*-toluidine using the reported conditions[20] were unsuccessful, with the only product isolated after a 24 hour reflux being the toluidide (261), formed by acetyl transfer from the acetate (260) to *p*-toluidine.



(261)

Substitution of the acetate group of (259) was attempted by reacting *p*-toluidine with the acetate in the presence of potassium carbonate (Scheme 79, conditions (b)). However, as for the previous attempt, the sole new product observed was the toluidide (261). It was recognized that besides displacement of the acetate group, other processes, such as elimination or nucleophilic attack at the carbonyl carbon atom, could occur during the course of the above reaction. Although acetate displacement has been reported[20] as being the major pathway when copper catalysis is used, attempts to reproduce this result with and without copper catalysis resulted only in attack at the acetate carbonyl carbon atom.

The coupling of propargyl phosphates such as (262) to aniline systems using copper catalysis has recently been reported,[20] but time constraints prevented the investigation of this pathway.

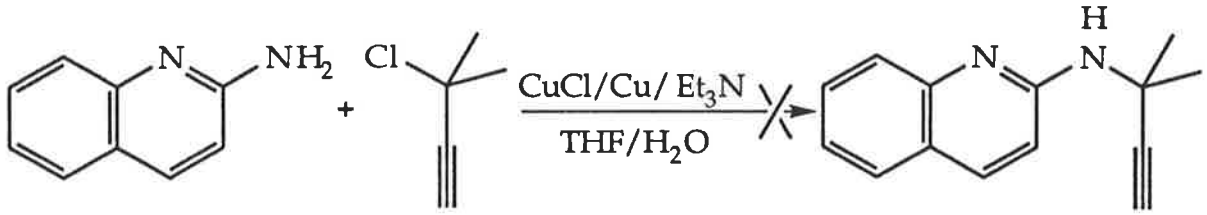


(262)

Also of interest was the behaviour of larger amino-substituted aromatic systems such as quinolines, naphthalenes and anthracenes towards the coupling and cyclization conditions.

Reaction of 2-aminoquinoline (89) with the chloroalkyne (61) (Scheme 80) was hindered due to immediate complexation of the copper catalyst with the aminoquinoline. Therefore, investigation was directed towards aminoquinolines with the

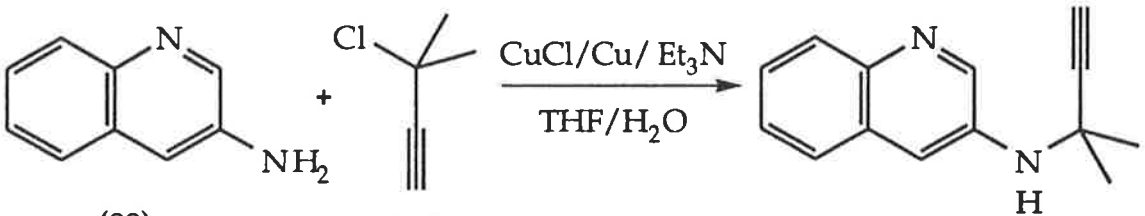
amino substituent further removed from the heterocyclic nitrogen atom, with the expectation that these latter compounds should be less likely to form copper complexes.



(89) (61) (263)

Scheme 80

The reaction of the chloroalkyne (61) with 3-aminoquinoline (88) proceeded much more smoothly than that of the 2-amino isomer to give a 63% yield of the N-propargyl aminoquinoline (264) (Scheme 81). The product (264) showed a singlet resonance at δ 2.44 in its ^1H nmr spectrum, attributed to the acetylenic hydrogen, and an infrared spectrum exhibited absorbances at 3650, 3300 and 1550 cm^{-1}, indicating the presence of NH, acetylenic hydrogen and C=N groups respectively.

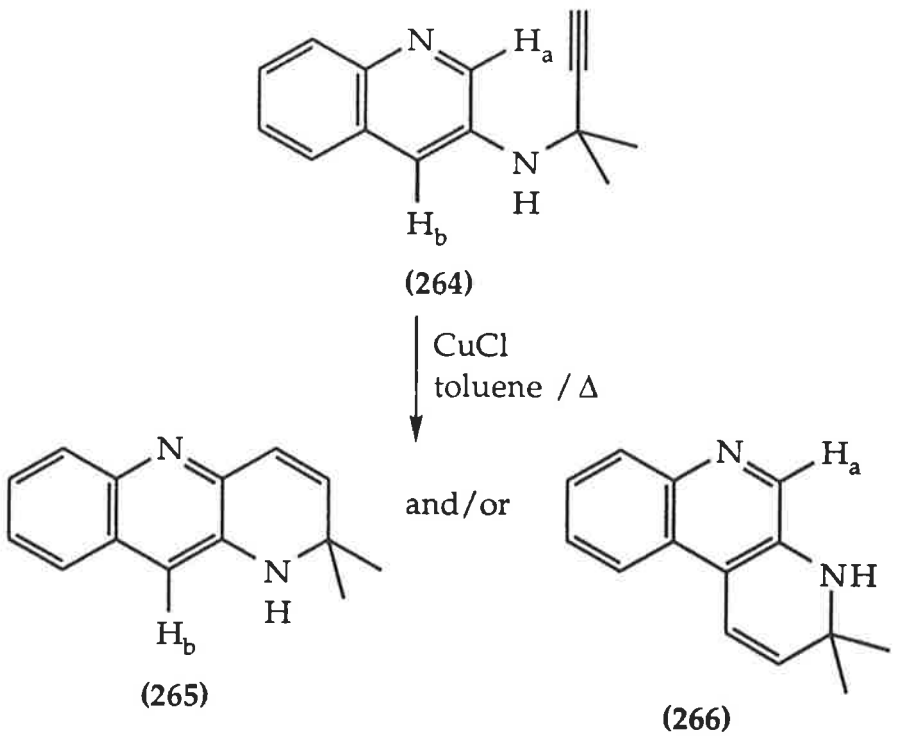


(88) (61) (264)

Scheme 81

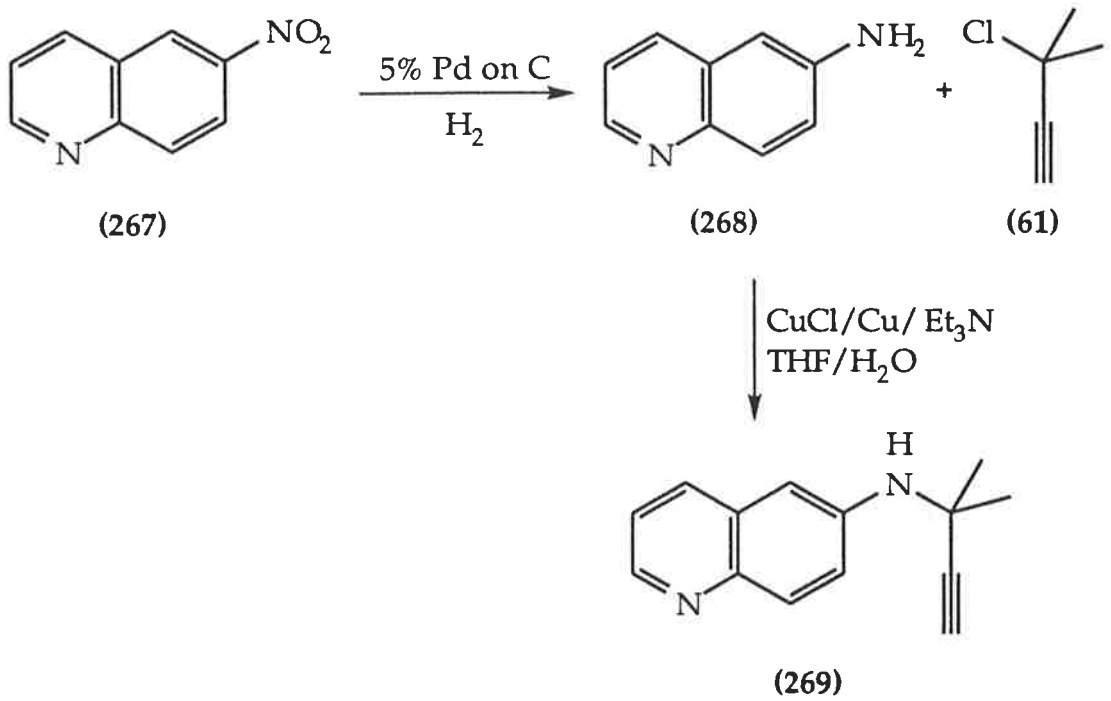
The cyclization of (264) (Scheme 82) proceeded to give exclusively one product. The cyclized product was identified as (266) by careful analysis of the

aromatic region of its ^1H nmr spectrum. A feature common to the ^1H nmr spectra of the starting N-propargyl compound (264) and the cyclized material (266) was the presence of a signal at approximately δ 8.4, attributed to the hydrogen adjacent to the heterocyclic nitrogen atom (H_a). If the alkyne (264) had cyclized to the alternate structure (265), a signal for H_a would not have been observed in the ^1H nmr spectrum of the product. The presence of such a signal in the cyclized product suggested that the structure is that of (266). Also supporting the structure (266) was the absence of a signal in the ^1H nmr spectrum for H_b, which was observed in the starting material (264) at δ 7.63. The ^1H nmr spectrum of (266) also showed the two signals expected for the two hydrogen atoms on the newly-formed double bond at δ 5.74 and 6.94. However, the splitting pattern of the signal at δ 5.74 was not the expected doublet, but rather a doublet of doublets, which was attributed to coupling with the adjacent olefinic hydrogen and a W-coupling to the hydrogen of the NH group.



Scheme 82

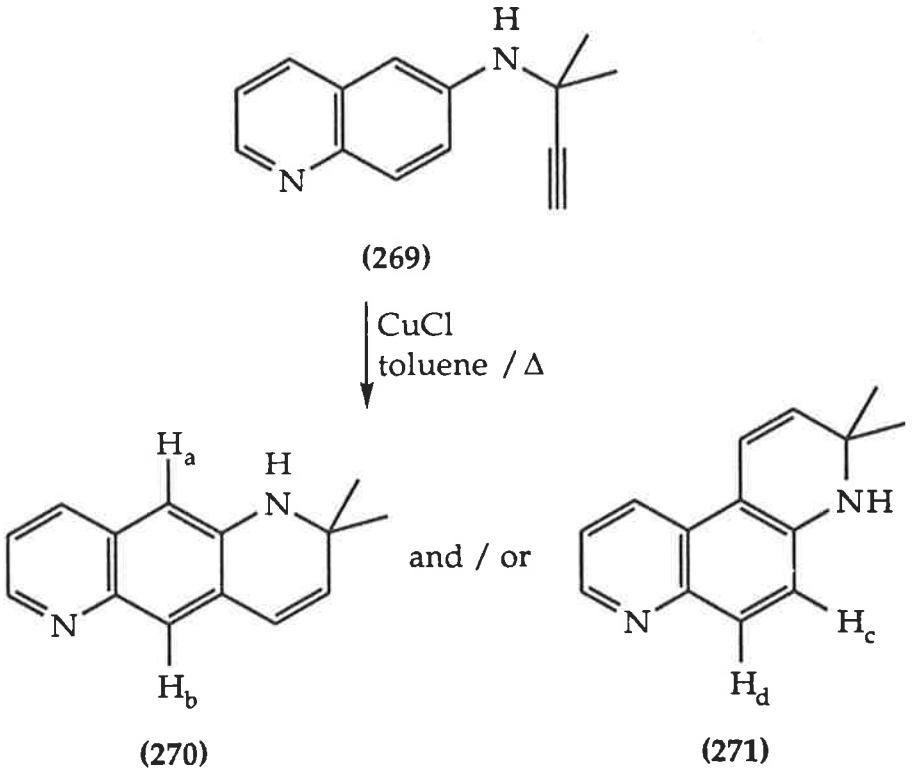
6-Aminoquinoline (268), obtained from the corresponding nitroquinoline (267) by hydrogenation, was coupled to the chloroalkyne (61) to give the N-propargyl aminoquinoline (269) (Scheme 83). A ^1H nmr spectrum of (269) showed singlets at δ 1.67 and 2.44, assigned to the hydrogens of the two equivalent geminal methyl groups and the acetylenic hydrogen atom respectively. A mass spectrum of (269) gave a peak at m/z 211, corresponding to an M+H ion for the molecule.



Scheme 83

The alkyne (269) was treated with cuprous chloride in refluxing toluene (Scheme 84) to give only one cyclized product. The ^1H nmr spectrum of this product showed two doublets at δ 6.93 (J 9 Hz) and 7.65 (J 9 Hz), assigned to H_c and H_d on the benzene ring of the molecule. This splitting pattern allowed the structure of the cyclized material to be identified as that of (271), since the

other possible structure (270) would not show two doublets with a large coupling constant in this region, but rather two singlets for H_a and H_b. Also present in the ^1H nmr spectrum of (271) were the signals at δ 5.35 and 6.87 for the olefinic hydrogens on the newly-formed double bond. As for the related structure (266), the signal at δ 5.35 was not the expected doublet but a doublet of doublets, again attributed to a vicinal and a W-coupling.

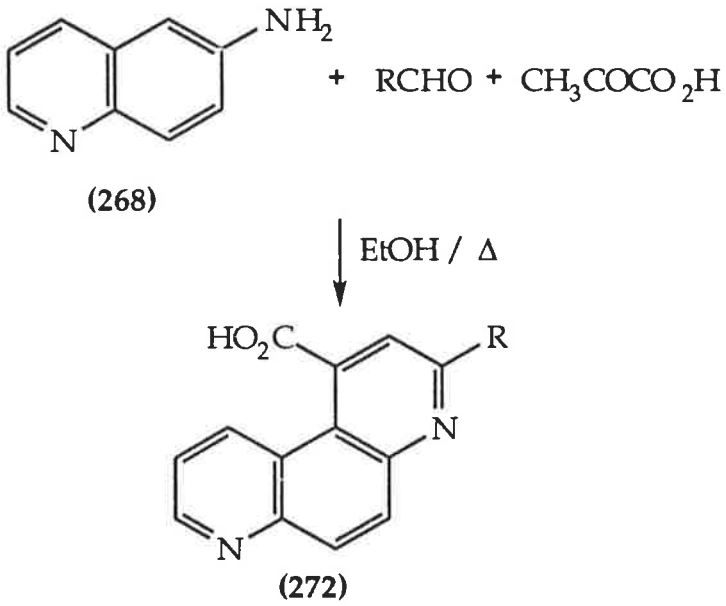


Scheme 84

The preference for one cyclization site was attributed to bond fixation, which is seen in naphthalenes and related systems. Due to the different resonance contributors present in such systems, the 1,2 carbon-carbon bond has more double bond character than the 2,3 carbon-carbon bond. This renders the C 1

carbon atom more nucleophilic than the C 3 carbon atom, which means that cyclization onto the C 1 site will be preferred over cyclization onto the C 3 site.

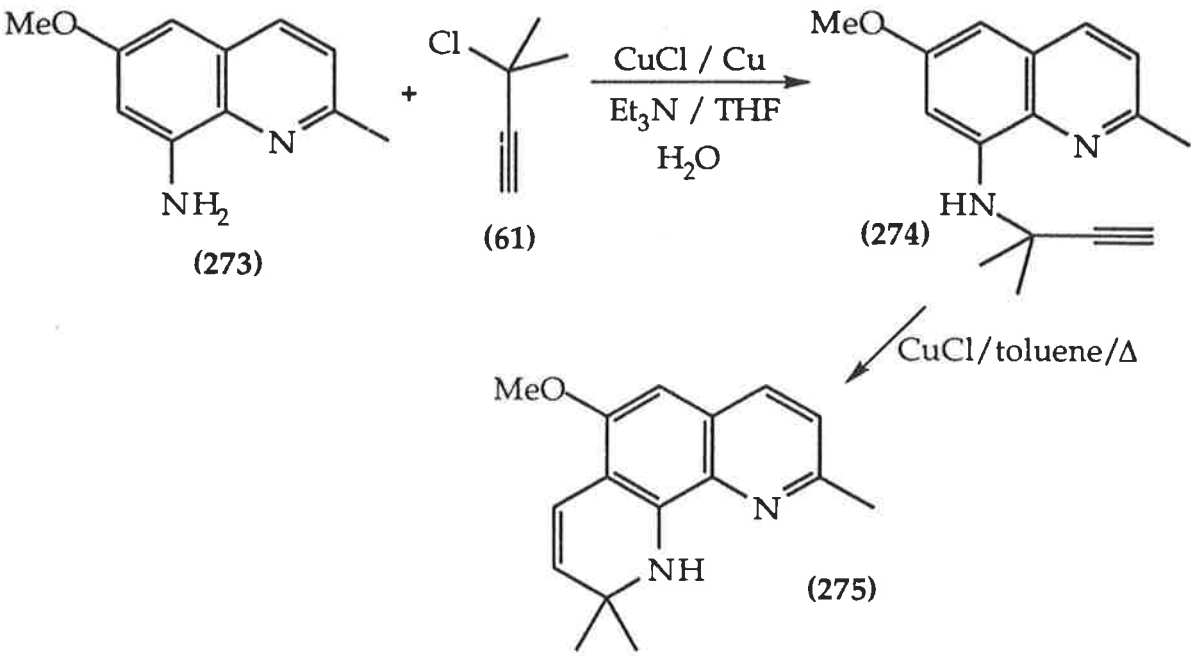
Examples of systems similar to (264) and (269) showing a preference for one cyclization site have been cited in the literature,[60-64] with an example being the reaction[60-62] of 6-aminoquinoline (268) with an aldehyde and a 2-keto carboxylic acid to give the 4,7-phenanthroline (272) as the major product (Scheme 85).



Scheme 85

A sample of the 8-aminoquinoline[83] (273) was available from other work within our group, so it was decided to test the reactivity of this system towards coupling and cyclization. Reaction of (273) with the chloroalkyne (61) (Scheme 86) gave only a low yield of the N-substituted aminoquinoline (274), since the progress of the reaction was hampered by copper complexation. This problem was not unexpected, since systems such as (273) were synthesized

with the specific purpose to complex with metal cations. ^1H nmr of the alkyne (274) showed resonances at δ 1.77 for the hydrogens of the two equivalent geminal methyl groups, δ 2.41 for the acetylenic hydrogen and δ 2.64 for the hydrogens of the methyl group on the heterocyclic ring.



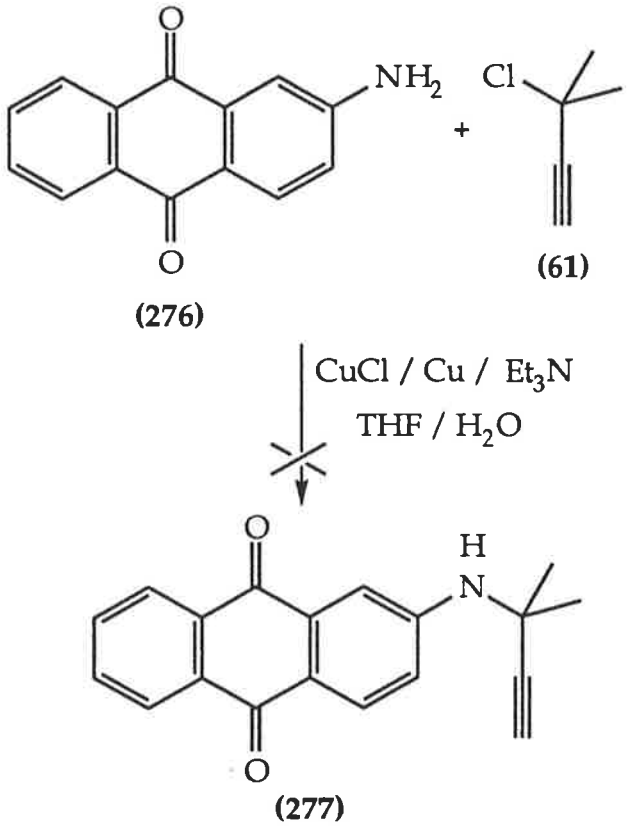
Scheme 86

Cyclization of the N-substituted quinoline (274) (Scheme 86) proceeded to give a 30% yield of the phenanthroline (275). The low yield was again attributed to the tendency of the 8-aminoquinoline system to complex with the copper catalyst. A ^1H nmr spectrum of the cyclized material showed signals at δ 5.48 and 6.73 for the hydrogens on the newly-formed double bond. The signal at δ 5.48, assigned to the hydrogen H_a, was observed as a doublet of doublets which was attributed to a vicinal coupling to the adjacent olefinic hydrogen and a W-coupling to the NH, as seen for the similar systems (266) and (271). The product (275) also showed singlets in the ^1H nmr at δ 2.64 and 3.89

corresponding to the hydrogens of the aryl methyl group and the methoxy group respectively.

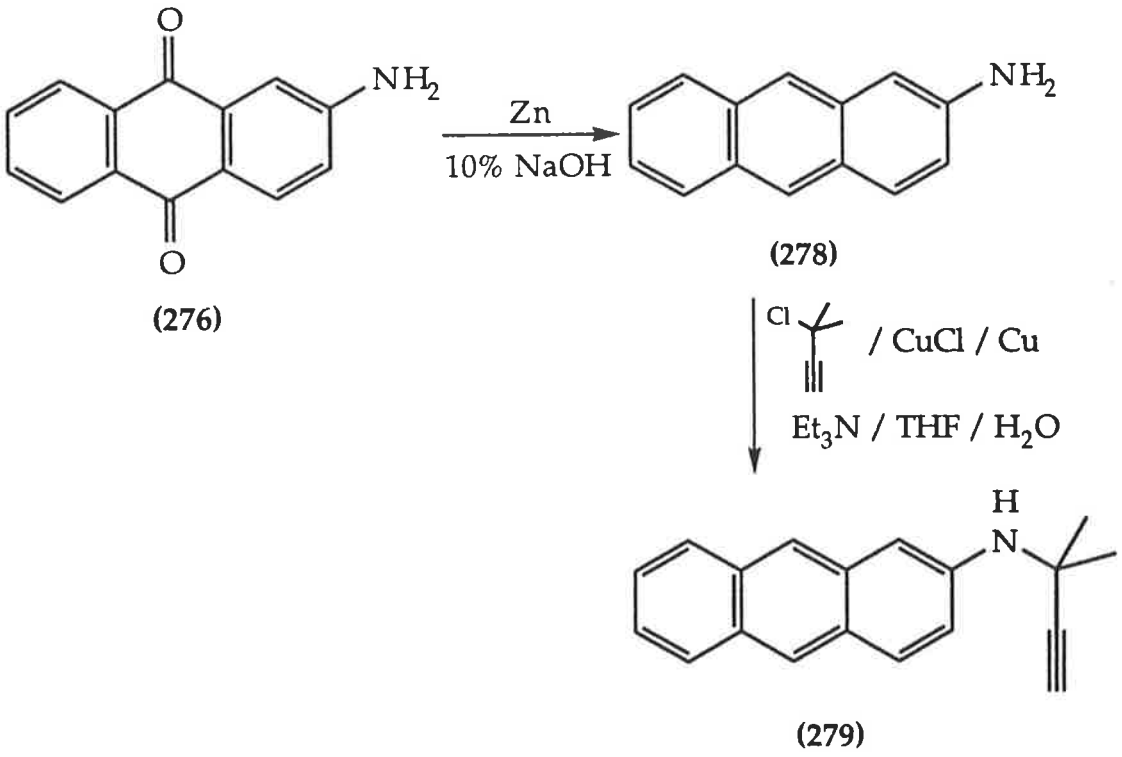
The use of aminonaphthalenes such as (86) and (87) (see page 29) in the coupling and cyclization reactions was considered, but rejected due to the extreme carcinogenicity of these compounds. However, a study was made of the coupling and cyclization reactions using anthraquinone and anthracene systems.

Attempts to couple the aminoanthraquinone (276) to the chloroalkyne (61) resulted in the formation of only trace amounts of the desired N-propargyl compound (277) (Scheme 87). The failure of this reaction was attributed to the electron withdrawing effect of the carbonyl groups of the anthraquinone reducing the nucleophilicity of the nitrogen atom to that equivalent to an amide, making the reaction unfavourable.



Scheme 87

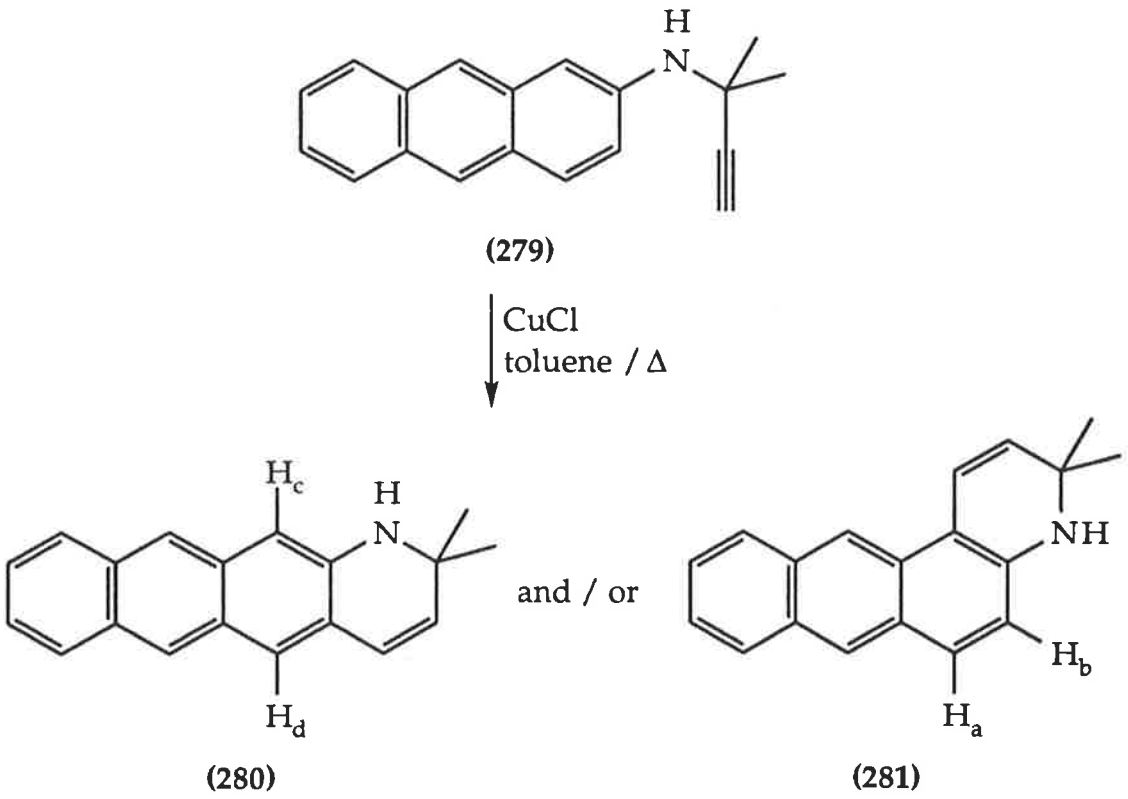
Reduction of the aminoanthraquinone (276) to the aminoanthracene (278) was achieved using a reported procedure[65] (Scheme 88). ^{1}H nmr of the product anthracene (278) exhibited two singlets at δ 8.11 and 8.28, assigned to the two hydrogens of the central aromatic ring, the presence of which confirmed the success of the reduction. Reaction of (278) with the chloroalkyne (61) gave the coupled product (279) in a 22% yield. The low yield was caused by difficulties encountered during the purification of (279), which needed to be separated from numerous other reaction products. This problem suggested that the aminoanthracene system was not as suited to the coupling conditions as its aniline counterpart, which generally underwent reaction smoothly. A ^{1}H nmr spectrum of the product (279) showed singlet resonances at δ 1.70 and 2.45, assigned to the hydrogens of the geminal dimethyl groups and the acetylenic hydrogen respectively, as well as aromatic signals consistent with those expected for a 2-substituted anthracene.



(276) (278) (279)

Scheme 88

Cyclization of the alkyne (279) (Scheme 88) gave exclusively one product, whose ^1H nmr spectrum showed two doublets at δ 6.74 and 7.68 with a coupling constant of 9.0 Hz, assigned to the hydrogens H_a and H_b. This distinguishing feature allowed positive identification of the cyclized product as (281), since the alternative structure (280) would have exhibited two singlets corresponding to H_c and H_d in its ^1H nmr spectrum. Also present in the ^1H nmr spectrum of (281) were two signals at δ 5.54 and 7.13 for the hydrogens on the newly-formed double bond. The signal at δ 5.54 was split into a doublet of doublets; presumably by a vicinal and a W-coupling as was observed for the corresponding hydrogen atoms of the phenanthrolines (266) and (271). The preference for one cyclization site over another was again attributed to bond fixation (see page 106).



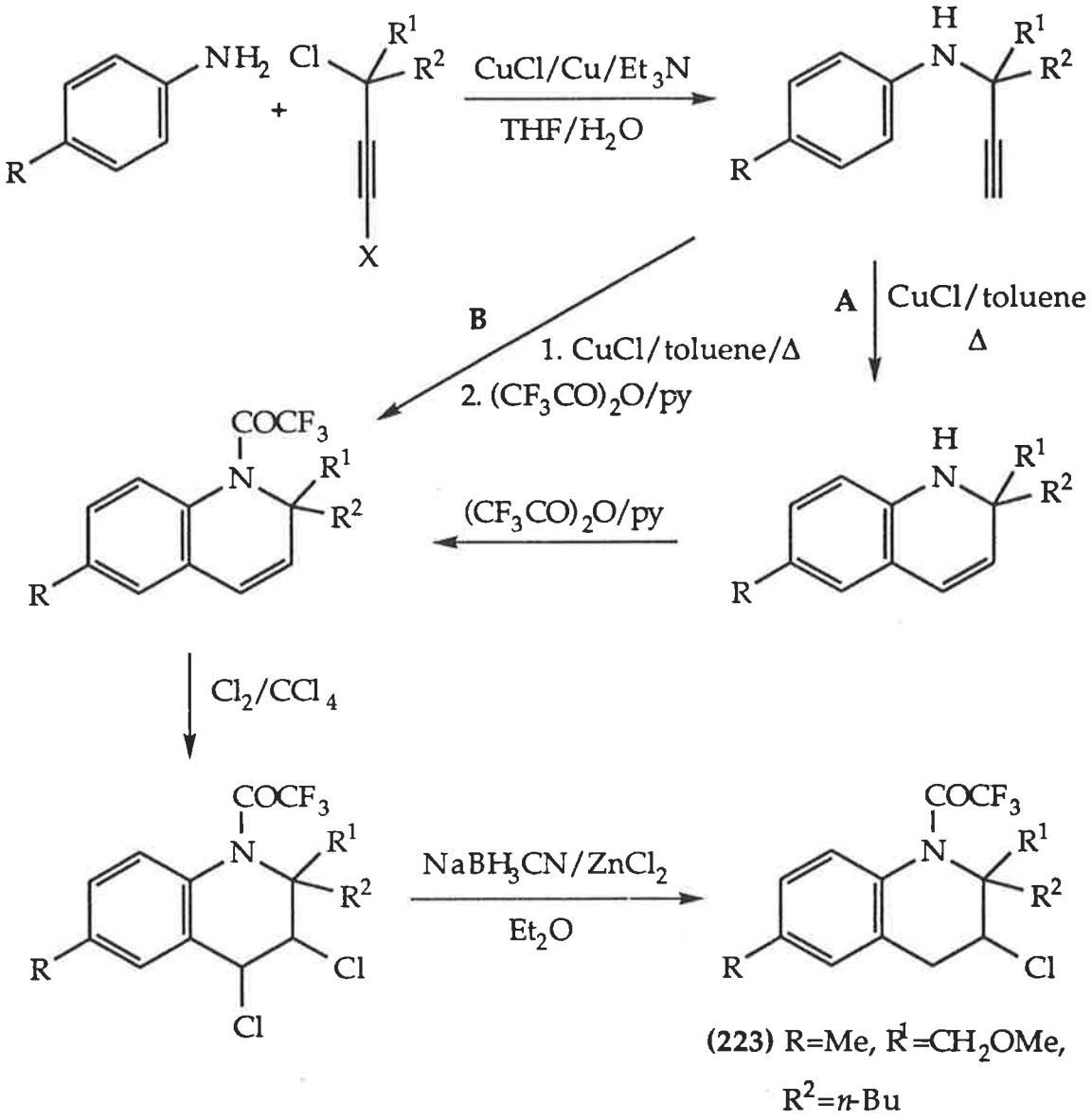
Scheme 89

The work described in this chapter has shown that the coupling and cyclization reactions are applicable to a wide range of systems, including *ortho*- and *meta*-substituted anilines, aminoquinolines and aminoanthracenes.

Chapter 5 - Conclusions and Future Investigations

This thesis has reported a general procedure for the synthesis of virantmycin analogues. The 5-step sequence (Scheme 90, page 114), in which the key step was the copper-catalyzed cyclization of an N-propargyl aniline system, was utilized to synthesize a wide range of 2,2-dimethyl-substituted analogues with a number of different substituents on the aromatic ring (Route A). Substituents incorporated included methoxy, hydroxy, amido and halogeno groups. A similar sequence of reactions (Route B) was used to synthesize the 2-butyl-2-methoxymethyl-6-methylsubstituted analogue (223), whose side chains more closely resemble those of virantmycin. The successful preparation of the virantmycin analogues (190), (216)-(222) and (223) shows that the reaction sequence used to synthesize them is tolerant of both larger side chains α- to the nitrogen atom and a large variety of substituents on the aromatic ring. 2,2-Dibutylsubstituted systems could not be synthesized *via* this route, however, because the steric bulk of the two butyl groups was enough to prevent the initial coupling from occurring.

A detailed study of the cyclization reaction found that electron donating substituents accelerate the reaction, while electron withdrawing substituents decrease the rate of reaction. For 2-methoxymethyl-2-butylsubstituted systems, the cyclization was successful only when the aromatic ring bore an electron donating substituent. The cyclization reaction was not only applied to *p*-substituted aniline based systems, but extended to *o*- and *m*-substituted aniline, aminoquinoline and aminoanthracene based systems, which gave the expected polycyclic compounds on cyclization. These results demonstrate the versatility of the cyclization reaction.



Scheme 90

Although the reaction sequence used in this work to synthesize virantmycin analogues includes reactions that should preclude any stereoselectivity, it appears that some selectivity occurs when the substituents in the 2-position are methoxymethyl and *n*-butyl. N. O. e. studies of the chloro compound (223) suggested that the chlorine atom and the methoxymethyl group exist in

a *cis* arrangement in the molecule. Future work could include the synthesis of the single diastereomers of (223) by a different route.

Further investigations could also be carried out on the behaviour of the iodo-substituted dihydroquinoline (189) towards palladium-catalyzed reactions. A brief study was included in this work, but time restraints prevented a more detailed investigation. Heck conditions should, once optimized, be able to couple a variety of alkenes to the iodo-substituted dihydroquinoline (189) or its derivatives. Such coupled products could then be manipulated to give other useful functional groups; for example, ozonolysis would produce an aldehyde-substituted dihydroquinoline, which would be difficult to synthesize *via* the coupling and cyclization reactions reported here because of the electron withdrawing nature of the aldehyde group and the tendency of aminoaldehydes towards self-condensation.

Another area that warrants further study is the chemistry of the double bond of the N-acyl dihydroquinoline system. It would be of interest to see how reactive the double bond is, for example, towards ozonolysis, oxymercuration, hydroboration and osmium tetroxide.

Experimental

General

Melting points were determined on a Kofler hot stage apparatus equipped with a Reichert microscope and are uncorrected.

Microanalyses were performed by Chemical and Microanalytical Services, Pty. Ltd., Melbourne or the University of Otago.

Ether refers to diethyl ether. Light petroleum refers to the fraction of boiling range 66-68°. Dry ether and tetrahydrofuran were distilled from sodium/benzophenone ketyl prior to use. Drying and/or purification of other organic solvents was achieved using standard laboratory procedures.[84, 85] All organic extracts were dried over magnesium sulphate unless otherwise indicated.

Analytical thin layer chromatography (tlc) was carried out using Merck Kieselgel $60F_{254}$ silica on aluminium-backed plates. Flash chromatography[86] refers to nitrogen-pressure driven rapid chromatography using Merck silica gel, pore diameter 60Å.

Infrared spectra were recorded on a Jasco A102 grating spectrometer. Proton nuclear magnetic resonance (^{1}H nmr) spectra were recorded on a Bruker ACP300 spectrometer operating at 300MHz, in deuterochloroform solution unless otherwise specified, with tetramethylsilane used as an internal standard. All chemical shifts are quoted as δ in parts per million and coupling constants (J) are given in Hertz (Hz). Where the extremities of a multiplet are

well defined, a range is given, otherwise a value for the centre of the signal is recorded. Multiplicities are abbreviated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

Electron impact mass spectra were recorded at 70eV on a VG ZAB 2HF spectrometer. Only the major fragments are given with their relative abundances shown in parentheses. Accurate mass measurements were made either on an AEI MS3074 spectrometer or by Melbourne University on a JEOL AX505H spectrometer.

Chapter 1

3-Chloro-3-methyl-1-butyne (61)

2-Methyl-3-butyn-2-ol (16.84 g, 200 mmol) was added dropwise over 15 min to a stirred solution of cuprous chloride (8.0 g, 81 mmol) and calcium chloride (9.2 g, 83 mmol) in concentrated hydrochloric acid (86 ml) cooled to 0°. Stirring at this temperature was continued for a further hour. The organic layer was separated, washed with cold, concentrated hydrochloric acid (3x50 ml), dried and distilled to give the *chloroalkyne* (61) (13.74 g, 67%) as a colourless liquid, bp 74-76° (lit.[16] 73-76°). ν_{max} (neat film): 3275 (C≡CH); 2100 (C≡C); 780 cm^{-1} (C-Cl). ^1H nmr: δ 1.85, s, 2xCH_3; 2.60, s, C≡CH. Mass spectrum *m/z* 102/104 (M, 50%).

Methoxyacetyl chloride (97)

Methoxyacetic acid (15 g, 170 mmol) and thionyl chloride (29.76 g, 250 mmol) were refluxed at 110-120° under an atmosphere of nitrogen for 2 h. The mixture was fractionally distilled through a 20cm Vigreux column to yield the *acid chloride* (97) (11.40 g, 63%) as a colourless liquid, bp 109-113° (lit.[15] 105-110°). ν_{max} (neat film): 1800 (C=O); 1200, 1130 (C=O); 750 cm^{-1} (C-Cl). ^1H nmr: δ 3.50, s, CH_3O; 4.38, s, OCH_2.

1-Bromo-2-hexanol (103)

A solution of 1-hexene (6.73 g, 80 mmol) and water (2.9 ml, 161 mmol) in dimethylsulphoxide (100 ml) was cooled to 10°. With stirring, N-bromosuccinimide (29.0 g, 163 mmol) was added in one portion. The mixture was stirred at ambient temperature for 1 h, poured into dilute aqueous sodium bicarbonate solution (200 ml) and extracted with ether (2x50 ml). The combined organic extracts were washed with water (3x50 ml), dried and the solvent removed to give the *bromohydrin* (103) (13.92 g, 96%) as a pale yellow oil. ν_{max} (neat film): 3000-3500 (OH); 1040 cm^{-1} (C-O). ^1H nmr: δ 0.92, t, J 6.8 Hz, CH_3; 1.3-1.6, m, 3xCH_2; 2.34, br s (exchanges with D_2O), OH; 3.39, dd, J 7.0, 10.4 Hz, 1H of CH_2Br; 3.55, dd, J 3.2, 10.4 Hz, 1H of CH_2Br; 3.79, m, C<u>H</u>OH. Mass spectrum *m/z* 179/181 (M, 1%); 163/165 (50); 123/125 (30); 87 (100).

The crude bromohydrin (103) was of sufficient purity to be used directly in the next reaction.

1-Methoxy-2-hexanol (104)

Sodium (0.84 g, 36 mmol) was added portionwise to a solution of the bromohydrin (103) (3.29 g, 18 mmol) in dry methanol (20 ml) and the resulting mixture refluxed under an atmosphere of nitrogen for 3 h. The reaction mixture was cooled, water (20 ml) added and the resulting solution extracted with dichloromethane (3x20 ml). The combined organic extracts were dried and the solvent removed to yield the *methoxyalcohol* (104) (2.00 g, 84%) as a pale yellow oil. ν_{max} (neat film): 3000-3500 (OH); 1060 cm^{-1} (C-O). ^1H nmr: δ 0.91, t, J 7.3 Hz, CH_3; 1.3-1.5, m, 3xCH_2; 2.66, br s (exchanges with D_2O), OH; 3.24, dd, J 8.0, 9.6 Hz, 1H of OCH_2; 3.39, s, OCH_3; 3.41, dd, J 8.0,

9.6 Hz, 1H of OCH_2; 3.78, m, C<u>H</u>OH. Mass spectrum *m/z* 131 (M-H, 2%); 115 (20); 87 (50); 69 (100).

The crude methoxyalcohol (104) was of sufficient purity to use directly in the next reaction.

1-Methoxy-2-hexanone (98)

1. Oxidation of methoxyalcohol (104)

Jones reagent was added dropwise to a stirred solution of the methoxyalcohol (104) (5.09 g, 39 mmol) in acetone (30 ml) until the orange colour just persisted. The acetone was removed under reduced pressure, the residue treated with water (75 ml) and extracted with dichloromethane (3x40 ml). The combined organic extracts were washed with water (100 ml), dried and the solvent removed. The residue was distilled to afford the *ketone* (98) (3.46 g, 69%) as a colourless oil, bp 82-86°/30mm. ^1H nmr: δ 0.91, t, J 7.3 Hz, CH_3; 1.25-1.7, m, 2xCH_2; 2.43, t, 7.4 Hz, CH_2; 3.42, s, OCH_3; 4.03, s, OCH_2. Mass spectrum *m/z* 129 (M-H, 50%); 97 (10); 85 (50); 81 (50); 69 (100).

2. Reaction of methoxyacetyl chloride (97) with butylmanganese bromide

Butylmagnesium bromide in ether (3.43M; 35 ml, 110 mmol) was added dropwise to a rapidly stirred suspension of manganese iodide (34.15 g, 110 mmol) in dry ether (150 ml) at 0°. The resulting mixture was stirred at 0-5° for 10 min and at ambient temperature for 30 min. After cooling to -60°, a solution of the acid chloride (97) (10 g, 90 mmol) in dry ether (25 ml) was added over 45 min. The mixture was allowed to warm, with stirring, to ambient temperature overnight. The reaction mixture was quenched

with 5% hydrochloric acid (100 ml) and extracted with ether (2x70 ml). The combined organic extracts were washed with 10% sodium thiosulphate (60 ml) and saturated sodium bicarbonate (60 ml), dried and the solvent removed. The residue was distilled to yield the *ketone* (98) (2.09 g, 18%) as a yellow oil with spectral characteristics identical to those of the product formed from the previous reaction.

3-Methoxymethyl-1-trimethylsilylhept-1-yn-3-ol (99)

Butyllithium (2.5M in hexanes; 8.5 ml, 21 mmol) was added dropwise to a stirred solution of trimethylsilylacetylene (2.26 g, 23 mmol) in dry tetrahydrofuran (40 ml) at -70°. The resulting solution was stirred at this temperature for 10 min, followed by the slow addition of the ketone (98) (2.50 g, 19 mmol) in dry tetrahydrofuran (10 ml) at -70°. The mixture was stirred at -70° for 30 min and then quenched at this temperature with saturated ammonium chloride (40 ml). The organic phase was separated and combined with ethereal extracts of the aqueous phase. The combined organic extracts were dried and the solvent removed. The residue was distilled to give the *alkynol* (99) (2.16 g, 50%) as a colourless liquid, bp 52-54°/0.03mm. ν_{max} (neat film): 3200-3600 (OH); 2140 (C≡C); 1250 cm^{-1} ($Si(CH_3)_3$). ^1H nmr: δ 0.17, s, $Si(CH_3)_3$; 0.92, t, J 7.3 Hz, CH_3; 1.3-1.7, m, $3xCH_2$; 2.80, br s (exchanges with D_2O), OH; 3.38, d, J 9.3 Hz, 1H of OCH_2; 3.46, s, OCH_3; 3.48, d, J 9.3 Hz, 1H of OCH_2. Mass spectrum *m/z* 212 (M-O, 30%); 211, (M-OH, 100); 184 (40); 183 (100).

3-Chloro-3-methoxymethyl-1-trimethylsilyl-1-hexyne (100)

The alkynol (99) (4.35 g, 19 mmol) was added to a stirred mixture of cuprous chloride (0.79 g, 7.9 mmol), calcium chloride (1.06 g, 9.5 mmol) and copper bronze powder (0.60 g) in concentrated hydrochloric acid (50 ml) and the resulting mixture stirred at ambient temperature for 96 h. The mixture was extracted with dichloromethane (3x40 ml); the combined organic extracts were washed with concentrated hydrochloric acid (2x40 ml) and water (3x30 ml), dried and the solvent removed. The residue was purified by flash chromatography; elution with light petroleum/ethyl acetate (95:5) afforded the *chloroalkyne* (100) (3.44 g, 73%) as a colourless oil. (Found: 246.1194. $C_{12}H_{23}ClOSi$ requires 246.1207.) ^1H nmr: δ 0.18, s, $Si(CH_3)_3$; 0.94, t, J 7.3 Hz, CH_3; 1.3-1.4, m, CH_2; 1.5-1.6, m, CH_2; 1.9-2.0, m, CH_2; 3.49, s, OCH_3; 3.64, s, OCH_2. Mass spectrum *m/z* 247/249 (M+H, 15%); 231/233 (15); 211 (100); 180 (80).

3-Butyl-1-trimethylsilylhept-1-yn-3-ol (109)

Butyllithium (2.5M in hexanes; 3.10 ml, 7.7 mmol) was added dropwise to a stirred solution of trimethylsilylacetylene (0.83 g, 8.5 mmol) in dry tetrahydrofuran (15 ml) at -70°. The resulting mixture was stirred at this temperature for 10 min, followed by the slow addition of a solution of 5-nonanone (1.00 g, 7 mmol) in dry tetrahydrofuran (5 ml) at -70°. The mixture was stirred at this temperature for 20 min and quenched by the addition of saturated ammonium chloride (15 ml). The organic phase was separated and combined with ethereal extracts of the aqueous phase. 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) provided the *alkynol* (109) (1.42 g, 85%) as a colourless oil. ν_{max} (neat film):

3250-3600 (OH); 2135 (C≡C); 1255 cm^{-1} ($Si(CH_3)_3$). ^1H nmr: δ 0.16, s, $Si(CH_3)_3$; 0.93, t, J 6.8 Hz, $2xCH_3$; 1.25-1.75, m, $4xCH_2$; 2.10, br s (exchanges with D_2O), OH; 2.40, t, J 7.3 Hz, $2xCH_2$. Mass spectrum *m/z* 223 (M-OH, 80%); 183 (100); 150 (15).

3-Butyl-3-chloro-1-trimethylsilyl-1-heptyne (110)

The dibutylalcohol (109) (1.19 g, 5 mmol) was added to a stirred mixture of cuprous chloride (0.21 g, 2.1 mmol), calcium chloride (0.28 g, 2.5 mmol) and copper bronze powder (0.20 g) in concentrated hydrochloric acid (30 ml) and the resulting mixture stirred at ambient temperature for 48 h. The mixture was extracted with dichloromethane (3x20 ml) and the combined organic extracts were washed with concentrated hydrochloric acid (2x15 ml) and water (3x10 ml), dried and the solvent removed. The residue was purified by flash chromatography; elution with light petroleum/ethyl acetate (95:5) gave the *chloroalkyne* (110) (1.17 g, 91%) as a colourless oil. (Found: 258.1571. $C_{14}H_{17}ClSi$ requires 258.1570.) ν_{max} (neat film): 2140 (C≡C); 1250 cm^{-1} ($Si(CH_3)_3$). ^1H nmr: δ 0.18, s, $Si(CH_3)_3$; 0.94, t, J 7.3 Hz, $2xCH_3$; 1.25-1.7, m, $4xCH_2$; 1.89, m, $2xCH_2$. Mass spectrum *m/z* 258/260 (M, 10%); 243/245 (15); 225 (45); 224 (100); 223 (100).

N-Trifluoroacetyl-p-toluidine (111)

Trifluoroacetic anhydride (19.8 ml, 140 mmol) was added dropwise under an atmosphere of nitrogen to a stirred solution of *p*-toluidine (10 g, 93 mmol) and pyridine (40 ml) in dry dichloromethane (160 ml) cooled to 0°. The resulting mixture was allowed to warm, with stirring, to ambient temperature whereupon stirring was continued for a further hour. The

reaction was quenched by the careful addition of water (150 ml). The organic phase was separated, washed with 10% hydrochloric acid (5x40 ml) and water (2x40 ml), dried and the solvent removed. The solid residue was recrystallized from light petroleum to yield the *trifluoroacetamide* (111) (16.18 g, 85%) as pale yellow needles, mp 115.5-112°. ν_{max} (nujol mull): 3300 (NH); 1720 (C=O); 1610, 1507 cm^{-1} (C=C Ar). ^1H nmr: δ 2.34, s, CH_3; 7.18, d, J 8.4 Hz, 2xArH; 7.44, d, J 8.4 Hz, 2xArH; 8.02, br s (exchanges with D_2O), NH. Mass spectrum *m/z* 203 (M, 40%); 134 (35); 106 (100); 91 (50); 77 (80).

N-[4-(Trifluoroacetoxymethyl)-phenyl]-trifluoroacetamide (112)

A stirred mixture of the toluidide (111) (5.00 g, 25 mmol), potassium persulphate (23.9 g, 89 mmol) and cupric carbonate (12.2 g, 98 mmol) in trifluoroacetic acid (400 ml) was refluxed under an atmosphere of nitrogen for 24 h. The trifluoroacetic acid was removed by distillation and the residue dissolved in water and extracted with dichloromethane (3x100 ml). The combined organic extracts were washed with water (100 ml) and saturated sodium bicarbonate (2x100 ml), dried and the solvent removed. The solid residue was recrystallized from dichloromethane/light petroleum to afford the *trifluoroacetate* (112) (5.70 g, 71%) as pale yellow needles, mp 123-124°. ν_{max} (nujol mull): 3290 (NH); 1780 (C=O ester); 1710 (C=O amide); 1615, 1515 cm^{-1} (C=C Ar). ^1H nmr: δ 5.35, s, OCH_2; 7.45, d, J 8.5 Hz, 2xArH; 7.63, d, J 8.5 Hz, 2xArH; 7.96, br s (exchanges with D_2O), NH. Mass spectrum *m/z* 315 (M, 45%); 270 (25); 202 (100); 132 (50).

N-(4-Hydroxymethyl-phenyl)-trifluoroacetamide (113)

10% Aqueous potassium bicarbonate (139 ml, 139 mmol) was added slowly to a stirred solution of the trifluoroacetate (112) (4.88 g, 16 mmol) in methanol (100 ml). The resulting mixture was stirred at ambient temperature for 1.5 h then diluted with water (100 ml) and extracted with ethyl acetate (3x50 ml). The combined organic extracts were dried and the solvent removed. The solid residue was recrystallized from dichloromethane/light petroleum to give the *amidoalcohol* (113) (2.37 g, 70%) as a pale yellow powder, mp 115-116°. (Found: 219.0522. $C_9H_8F_3NO_2$ requires 219.0507.) ν_{max} (nujol mull): 3490 (NH); 3100-3300 (OH); 1705 (C=O); 1610, 1510 cm^{-1} (C=C Ar). ^1H nmr: δ 1.78, br s (exchanges with D_2O), OH; 4.70, s, OCH_2; 7.39, d, J 8.4 Hz, 2xArH; 7.56, d, J 8.4 Hz, 2xArH; 8.01, br s (exchanges with D_2O), NH. Mass spectrum *m/z* 219 (M, 70%); 218 (M-H, 30); 190 (100); 150 (25); 149 (25).

4-Trifluoroacetamidobenzaldehyde (115)

1. Attempted preparation using Jones Reagent

Jones reagent was added dropwise to a stirred solution of the amidoalcohol (113) (0.16 g, 7 mmol) in acetone (10 ml) until the orange colour just persisted. The acetone was removed under reduced pressure, the residue dissolved in water (30 ml) and extracted with ethyl acetate (3x20 ml). The combined organic extracts were dried and the solvent removed to yield *N-trifluoroacetyl-p-aminobenzoic acid* (116) (0.11 g, 65%) as a pale yellow powder, mp 216-218°. ν_{max} (nujol mull): 3300 (NH); 2600-3100 (OH acid); 1700 (C=O acid); 1675 (C=O amide); 1600, 1510 cm^{-1} (C=C Ar). ^1H nmr (d_6-acetone): δ 7.89, d, J 8.9 Hz, 2xArH; 8.08, d, J8.9 Hz, 2xArH; 8.38, br s (exchanges with

D_2O), NH; 10.58, br s (exchanges with D_2O), CO_2H. Mass spectrum *m/z* 233 (M,20%); 212 (100); 164 (20); 136 (25).

2. *Using pyridinium chlorochromate*

A solution of the amidoalcohol (113) (0.10 g, 5 mmol) in dry ether (2 ml) was added in one portion to a stirred suspension of pyridinium chlorochromate[26] (0.15 g, 7 mmol) in dry dichloromethane (5 ml) and the resulting mixture stirred under an atmosphere of nitrogen at ambient temperature for 2.5 h. Dry ether (10 ml) was added and the supernatant decanted from the insoluble material. The residue was washed thoroughly with dry ether (3x10 ml) and the combined organic extracts were passed through a thin pad of celite. The solvent was removed to give the *amidoaldehyde* (115) (90 mg, 91%) as a yellow powder, mp 184-186°. (Found: 217.0344. $C_9H_6F_3NO_2$ requires 217.0351.) ν_{max} (nujol mull): 3400 (NH); 1715 (C=O aldehyde); 1680 (C=O amide); 1595, 1500cm^{-1} (C=C Ar). ^1H nmr: δ 7.93, s, 4xArH; 9.98, s, CHO; 10.04, br s (exchanges with D_2O), NH. Mass spectrum *m/z* 217 (M, 100%); 216 (M-H, 80), 168 (20); 148 (15); 146 (20).

Ethyl-(4-aminophenyl)acetate (120)

A mixture of 4-aminophenylacetic acid (5.0 g, 33 mmol), concentrated sulphuric acid (1.9 ml, 36 mmol) and ethanol (75 ml) was refluxed for 1 h. The mixture was cooled, diluted with dichloromethane (100 ml) and washed with saturated sodium bicarbonate solution (4x75 ml). The organic phase was dried and the solvent removed to yield an orange oil, which was crystallized from water to give the *ester* (120) (5.45 g, 93%) as colourless needles, mp 50-51° (lit[89] 51°). ν_{max} ($CDCl_3$ film): 3425, 3325 (NH_2); 1720 (C=O); 1600, 1500 cm^{-1}

(C=C Ar). ^{1}H nmr: δ 1.23, t, J 7.0 Hz, CH_3; 3.48, s, CH_2; 3.51, br s (exchanges with D_2O), NH_2; 4.12, q, J 7.0 Hz, OCH_2; 6.63, d, J 8.4 Hz, 2xArH; 7.06, d, J 8.4 Hz, 2xArH. Mass spectrum *m/z* 179 (M, 15%); 105 (100); 76 (5).

bis-p-*Trimethylsilylbenzene (122)*

A solution of *p*-dibromobenzene (2.40 g, 10 mmol) in dry tetrahydrofuran (5 ml) was added slowly under an atmosphere of nitrogen to a stirred mixture of magnesium (0.51 g, 23 mmol) and dry tetrahydrofuran (5 ml). The resulting Grignard mixture was refluxed for 2 h, followed by the slow addition of a solution of trimethylsilyl chloride (3.34 g, 31 mmol) in dry tetrahydrofuran (5 ml). After the addition was complete, the resulting mixture was refluxed for a further 2 h. The reaction was quenched with saturated ammonium chloride solution (50 ml) and extracted with dichloromethane (3x20 ml). The combined organic extracts were dried and the solvent removed. The solid residue was recrystallized from methanol to afford the *disilyl compound* (122) (1.13 g, 50%) as white needles, mp 92° (lit.[18] 88°). ^{1}H nmr: δ 0.26, s, 2x$Si(CH_3)_3$; 7.52, s, 4xArH. Mass spectrum *m/z* 222 (M, 15%); 208 (45); 207 (100); 149 (5); 73 (25).

p-*Trimethylsilylnitrobenzene (123)*

70% Nitric acid (3 ml, *ca* 40 mmol) was added dropwise over 20 min to a stirred solution of the disilyl compound (122) (2.16 g, 9.7 mmol) in acetic anhydride (10 ml) heated to 100° and the resulting blood red solution refluxed gently for 20 min. The mixture was cooled, poured into water (50 ml) and extracted with ether (3x30 ml). The combined organic extracts were washed with 10% sodium hydroxide (3x30 ml), water (40 ml) and brine (40 ml), dried

and the solvent removed. The residue was purified by flash chromotography; elution with light petroleum/ethyl acetate (70:30) gave the *nitro compound* (123) (0.89 g, 47%) as white needles, mp 37-38° (lit.[24] 36.5°). ^{1}H nmr: δ 0.32, s, $Si(CH_3)_3$; 7.69, d, J 8.5 Hz, 2xArH; 8.17, d, J 8.5 Hz, 2xArH. Mass spectrum *m/z* 195 (M, 5%); 180 (100); 134 (35); 119 (25).

p-*Trimethylsilylaniline (124)*

A mixture of the nitrobenzene (123) (0.89 g, 4.6 mmol) and 5% palladium on carbon (100 mg) in dry benzene (15 ml) was stirred under an atmosphere of hydrogen for 24 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/dichloromethane (20:80) yielded the *aniline* (124) (0.49 g, 65%) as a pale yellow oil. ν_{max} (neat film): 3425, 3350 (NH_2); 1615, 1500 (C=C Ar); 1260cm^{-1} ($Si(CH_3)_3$). ^{1}H nmr: δ 0.25, s, $Si(CH_3)_3$; 3.70, br s (exchanges with D_2O), NH_2; 6.71, d, J 8.3 Hz, 2xArH; 7.34, d, J 8.3 Hz, 2xArH. Mass spectrum *m/z* 165 (M, 45%); 151 (20); 150 (100); 120 (5); 106 (15).

General procedure for the synthesis of N-propargyl anilines

A solution of either chloroalkyne (61) or (100) (30 mmol) in tetrahydrofuran (5 ml) was added slowly to a stirred mixture of the aniline (20 mmol), triethylamine (30 mmol), cuprous chloride (100 mg) and copper bronze powder (100 mg) in tetrahydrofuran (15 ml) and water (1 ml). The resultant mixture was stirred under an atmosphere of nitrogen for 0.5-24 h. Water (15 ml) was added and the organic phase 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 provided the *N-substituted anilines.*

By this method, the following compounds were prepared:

N-(2-Methylbut-3-yn-2-yl)-4-methylaniline (72)

(2.89 g, 88%) as white needles, bp 95-100°/0.015mm, mp 37-38°. (Found: 173.1196. $C_{12}H_{15}N$ requires 173.1204.) ^1H nmr: δ 1.57, s, 2xCH_3; 2.25, s, ArCH_3; 2.34, s, C≡CH; 3.20, br s (exchanges with D_2O), NH; 6.88, d, J 8.0 Hz, 2xArH; 7.01, d, J 8.0 Hz, 2xArH. Mass spectrum *m/z* 173 (M, 65%); 158 (100); 107 (100), 106 (95).

N-(2-Methylbut-3-yn-2-yl)-4-methoxyaniline (74)

(2.95 g, 97%) as a yellow oil, bp 65-70°/0.1mm. (Found: C, 76.0; H, 8.1; N, 7.4. $C_{12}H_{15}NO$ requires C, 76.1; H, 8.0; N, 7.4%) ^1H nmr: δ 1.53, s, 2xCH_3; 2.34, s, C≡CH; 3.11, br s (exchanges with D_2O), NH; 3.75, s, OCH_3; 6.79, d, J 6.7 Hz, 2xArH; 6.96, d, J 6.7 Hz, 2xArH. Mass spectrum *m/z* 189 (M,75%); 174 (100); 123 (50); 122 (100).

Ethyl-N-(2-methylbut-3-yn-2-yl)-4-aminobenzoate (73)

(1.20 g, 43%), as a yellow oil, bp 115-120°/0.03mm. (Found: C, 72.5; H, 7.6; N, 6.1. $C_{14}H_{17}NO_2$ requires C, 72.7; H, 7.4; N, 6.1%) ^1H nmr: δ 1.35, t, J 6.9 Hz, $CH_2C\underline{H}_3$; 1.64, s, 2xCH_3; 2.41, s, C≡CH; 4.23, br s (exchanges with D_2O), NH; 4.31, q, J 6.9 Hz, $C\underline{H}_2CH_3$; 6.88, d, J 6.9 Hz, 2xArH; 7.88, d, J 6.9 Hz, 2xArH. Mass spectrum *m/z* 231 (M, 50%); 216 (100); 165 (25); 120 (90).

N-(2-Methylbut-3-yn-2-yl)-4-bromoaniline (137)

(0.44 g, 64%) as an orange oil. (Found: 237.0155. $C_{11}H_{12}BrN$ requires 237.0153.) ^1H nmr: δ 1.59, s, 2xCH_3; 2.38, s, C≡CH; 3.60, br s (exchanges with D_2O), NH; 6.82, d, J 8.8 Hz, 2xArH; 7.27, d, J 8.8 Hz, 2xArH. Mass spectrum *m/z* 237/239 (M, 80%); 222/224 (100); 170/172 (100); 144 (55).

N-(2-Methylbut-3-yn-2-yl)-4-aminophenol (139)

(0.47 g, 59%) as tan needles, mp 107-109°. (Found: 175.0992. $C_{11}H_{13}NO$ requires 175.0997.) ν_{max} (nujol mull): 3270 (NH); 2600-3200 (OH); 1600, 1500 cm^{-1} (C=C Ar). ^1H nmr: δ 1.52, s, 2xCH_3; 2.34, s, C≡CH; 4.45, br s (exchanges with D_2O), NH and OH; 6.71, d, J 8.8 Hz, 2xArH; 6.92, d, J 8.8 Hz, 2xArH. Mass spectrum *m/z* 175 (M, 50%); 160 (100); 109 (95); 108 (35).

N-(2-Methylbut-3-yn-2-yl)-4-aminoacetanilide (140)

(0.73 g, 51%) as a tan powder, mp 86-88°. (Found: 216.1257. $C_{13}H_{16}N_2O$ requires 216.1263.) ^1H nmr: δ 1.57, s, 2xCH_3; 2.10, s, $COCH_3$; 2.36, s, C≡CH; 3.50, br s (exchanges with D_2O), NH amine; 6.90, d, J 8.8 Hz, 2xArH; 7.31, d, J 8.8 Hz, 2xArH; 7.72, br s (exchanges with D_2O), NH amide. Mass spectrum *m/z* 216 (M, 60%); 201 (70); 149 (25); 108 (55); 107 (100).

N-(2-Methylbut-3-yn-2-yl)-4-trimethylsilylaniline (141)

(0.18 g, 51%) as a pale yellow oil. (Found: 231.1437. $C_{14}H_{21}NSi$ requires 231.1443.) ^1H nmr: δ 0.23, s, $Si(CH_3)_3$; 1.63, s, $2xCH_3$; 2.38, s, C≡CH; 3.78, br s (exchanges with D_2O), NH; 6.93, d, J 7.7 Hz, 2xArH; 7.35, d, J 7.7 Hz, 2xArH. Mass spectrum *m/z* 231 (M, 30%); 216 (100); 158 (15); 150 (50); 73 (55).

N-(2-Methylbut-3-yn-2-yl)-p-*phenylenediamine (138)*

(0.40 g, 25%) as an unstable red oil. (Found: 174.1163. $C_{11}H_{14}N_2$ requires 174.1157.) ^1H nmr: δ 1.50, s, $2xCH_3$; 2.32, s, C≡CH; 3.23, br s (exchanges with D_2O), NH and NH_2; 6.60, d, J 8.6 Hz, 2xArH; 6.88, d, J 8.6 Hz, 2xArH. Mass spectrum *m/z* 174 (M, 30%); 159 (25); 109 (25); 107 (100).

Also obtained from the same reaction was *N,N'*-bis-*(2-methylbut-3-yn-2-yl)*-p-*phenylenediamine* (148) (85 mg, 5%) as an unstable orange solid, mp 145-146°. (Found: 240.1633. $C_{16}H_{20}N_2$ requires 240.1626.) ^1H nmr: δ 1.54, s, $4xCH_3$; 2.34, s, 2xC≡CH; 3.0, br s (exchanges with D_2O), 2xNH; 6.90, s, 4xArH. Mass spectrum *m/z* 240 (M, 25%); 205 (25); 173 (50); 160 (25); 106 (100).

Ethyl [N-(2-methylbut-3-yn-2-yl)-4-aminophenyl] acetate (142)

(0.95 g, 46%) as an orange oil. (Found: 245.1414. $C_{15}H_{19}NO_2$ requires 245.1416.) ν_{max} ($CDCl_3$ film): 3400 (NH); 3275 (C≡CH); 2225 (C≡C); 1720 (C=O); 1610, 1510 cm^{-1} (C=C Ar). ^1H nmr: δ 1.25, t, J 7.1 Hz, CH_3; 1.60, s, $2xCH_3$; 2.36, s, C≡CH; 3.50, s, CH_2; 3.67, br s (exchanges with D_2O), NH; 4.13, q, J 7.1 Hz, OCH_2; 6.89, d, J 8.6 Hz, 2xArH; 7.11, d, J 8.6 Hz, 2xArH. Mass spectrum *m/z* 245 (M, 25%); 230 (70); 172 (15); 105 (100).

N-(2-Methylbut-3-yn-2-yl)-4-iodoaniline (143)

(1.35 g, 52%) as a light-sensitive, unstable red oil. (Found: 285.0033. $C_{11}H_{12}IN$ requires 285.0016.) ν_{max} (CH_2Cl_2 film): 3400 (NH); 3300 (C≡CH); 1600, 1500 cm^{-1} (C=C Ar). ^1H nmr: δ 1.59, s, 2xCH_3; 2.38, s, C≡CH; 3.72, br s (exchanges with D_2O), NH; 6.71, d, J 9.0 Hz, 2xArH; 7.44, d, J 9.0 Hz, 2xArH. Mass spectrum *m/z* 285 (M, 85%); 270 (100); 219 (80); 143 (32).

N-Methyl-N-(2-methylbut-3-yn-2-yl) aniline (150)

(0.19 g, 24%) as a pale yellow oil. (Found: 173.1209. $C_{12}H_{15}N$ requires 173.1204.) ν_{max} (neat film): 3250 (C≡CH); 1600, 1500cm^{-1} (C=C Ar). ^1H nmr: δ 1.40, s, 2xCH_3; 2.38, s, C≡CH; 2.85, s, NCH_3; 7.11-7.17, m, 1xArH; 7.24-7.35, m, 4xArH. Mass spectrum *m/z* 173 (M, 15%); 158 (100); 142 (10); 106 (30); 105 (30); 77 (35).

N-[3-(Methoxymethyl)hept-1-yn-3-yl]-4-methylaniline (152)

(1.20 g, 61%) as a yellow oil. (Found: 245.1787. $C_{16}H_{23}NO$ requires 245.1780.) ^1H nmr: δ 0.92, t, J 7.2 Hz, CH_3; 1.2-1.9, m, 3xCH_2; 2.25, s, ArCH_3; 2.42, s, C≡CH; 3.37, s, OCH_3; 3.48, d, J 9.2 Hz, 1H of OCH_2; 3.55, d, J 9.2 Hz, 1H of OCH_2; 3.85, br s (exchanges with D_2O), NH; 6.92, d, J 8.4 Hz, 2xArH; 6.98, d, J 8.4 Hz, 2xArH. Mass spectrum *m/z* 245 (M, 5%); 200 (100); 158 (10); 156 (10).

Ethyl N-[3-(methoxymethyl)hept-1-yn-3-yl]-4-aminobenzoate (154)

(50 mg, 41%) as an orange oil. (Found: 303.1818. $C_{18}H_{25}NO_3$ requires 303.1834.) ^{1}H nmr: δ 0.91, t, J 7.1 Hz, CH_3; 1.3-2.1, 3xCH_2; 1.35, t, J 7.1 Hz $OCH_2C\underline{H}_3$; 2.51, s, C≡CH; 3.38, s, OCH_3; 3.53, d, J 9.2 Hz, 1H of OCH_2; 3.62, d, J 9.2 Hz, 1H of OCH_2; 4.31, q, J 7.1 Hz, $OC\underline{H}_2CH_3$; 4.54, br s (exchanges with D_2O), NH; 6.92, d, J 8.8 Hz, 2xArH; 7.84, d, J 8.8 Hz, 2xArH. Mass spectrum *m/z* 303 (M, 1%); 259 (20); 258 (100); 230 (5); 185 (3).

N-[3-(Methoxymethyl)hept-1-yn-3-yl]-4-methoxyaniline (153)

(20 mg, 38%) as an orange oil. (Found: 261.1731. $C_{16}H_{23}NO_2$ requires 261.1729.) ν_{max} ($CDCl_3$ film): 3300 (C≡CH); 3125 (NH); 1600, 1505 (C=C Ar); 1105 cm^{-1} (C-O). ^{1}H nmr: δ 0.92, t, J 7.1 Hz, CH_3; 1.25-1.55, m, 2xCH_2; 1.65-1.85, m, CH_2; 2.41, s, C≡CH; 3.39, s, OCH_3; 3.43, d, J 9.2 Hz, 1H of OCH_2; 3.51, d, J 9.2 Hz, 1H of OCH_2; 3.65, br s (exchanges with D_2O), NH; 3.76, s, $ArOCH_3$; 6.78, d, J 8.8 Hz, 2xArH; 7.00, d, J 8.8 Hz, 2xArH. Mass spectrum *m/z* 261 (M, 10%); 216 (100); 172 (10); 158 (10); 122 (15).

N-[3-(Methoxymethyl)hept-1-yn-3-yl]-4-bromoaniline (155)

(0.30 g, 48%) as an orange oil. (Found: 309.0741. $C_{15}H_{20}BrNO$ requires 309.0728.) ^{1}H nmr: δ 0.92, t, J 7.3 Hz, CH_3; 1.3-1.9, m, 3xCH_2; 2.46, s, C≡CH; 2.70, br s (exchanges with D_2O), NH; 3.39, s, OCH_3; 3.49, d, J 9.3 Hz 1H of OCH_2; 3.57, d, J 9.3 Hz, 1H of OCH_2; 6.87, d, J 8.8 Hz, 2xArH; 7.26, d, J 8.8 Hz, 2xArH. Mass spectrum *m/z* 309/311 (M, 10%); 265/267 (20); 264/266 (100); 251 (15).

N-[3-(Methoxymethyl)hept-1-yn-3-yl]-4-acetamidoaniline (156)

(0.079 g, 69%) as pale yellow needles, mp 106-108°. (Found: 288.1846. $C_{17}H_{24}N_2O_2$ requires 288.1838.) ν_{max} ($CDCl_3$ film): 3440 (NH amide); 3370 (NH amine); 3300 (C≡CH); 1675 (C=O); 1600, 1505 cm^{-1} (C=C Ar). ^1H nmr: δ 0.92, t, J 7.0 Hz, CH_3; 1.2-1.9, m, 3xCH_2; 2.11, s, $COCH_3$; 2.45, s, C≡CH; 3.38, s, OCH_3; 3.47, d, J 9.2 Hz, 1H of OCH_2; 3.55, d, J 9.2 Hz, 1H of OCH_2; 3.9, br s (exchanges with D_2O), NH amine; 6.95, d, J 8.7 Hz, 2xArH; 7.30, d, J 8.7 Hz, 2xArH; 7.67, br s (exchanges with D_2O), NH amide. Mass spectrum *m/z* 288 (M, 25%); 244 (20); 243 (100); 231 (5); 201 (7); 149 (15).

Attempted synthesis of N-[5-(ethynyl)nonan-5-yl]-4-methylaniline (158)

The chloroalkyne (110) (41 mg, 0.16 mmol) in tetrahydrofuran (1 ml) was added to a stirred mixture of *p*-toluidine (17 mg, 0.16 mmol), cuprous chloride (20 mg), copper bronze powder (20 mg) and triethylamine (33 µl, 0.24 mmol) in tetrahydrofuran (5 ml) and water (100 µl) and the resulting mixture refluxed for 48 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 chromatography; elution with light petroleum/ethyl acetate (80:20) afforded the starting materials.

Attempted synthesis of [4-(2-methylbut-3-yn-2-ylamino)phenyl]methanol (151)

The chloroalkyne (61) (35 mg, 0.34 mmol) in tetrahydrofuran (1 ml) was added to a stirred mixture of the amidoalcohol (113) (50 mg, 0.23 mmol), cuprous chloride (20 mg), copper bronze powder (20 mg) and triethylamine (50 µl, 0.34 mmol) in tetrahydrofuran (5 ml) and water (100 µl) and the resulting mixture refluxed for 48 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 chromatography; elution with light petroleum/ethyl acetate (1:1) returned the starting materials.

Synthesis of (72) using $CuCl_2$

A solution of the chloroalkyne (61) (0.14 g, 1.4 mmol) in tetrahydrofuran (2 ml) was added slowly to a stirred mixture of *p*-toluidine (0.10 g, 0.94 mmol), cupric chloride (5 mg) and triethylamine (0.14 g, 1.4 mmol) in tetrahydrofuran (5 ml) and water (250 µl) and the resulting mixture stirred at ambient temperature for 2.5 h. Water (10 ml) was added and the organic phase separated and combined with the dichloromethane extracts of the aqueous phase. The combined organic extracts were dried and the solvent removed. ^1H nmr of the residue indicated the presence of the *N-substituted aniline* (72) as part of a complex mixture. Therefore, all N-substituted anilines were prepared using cuprous chloride as the catalyst, following the previously reported procedures.[10-13]

Chapter 2

N-(2-Methylbut-3-yn-2-yl)-4-trimethylsilyloxyaniline (161)

Trimethylsilyl chloride (0.54 ml, 4.2 mmol) was added dropwise under an atmosphere of nitrogen to a stirred solution of the N-substituted aniline (139) (0.74 g, 4.2 mmol) and pyridine (0.68 ml, 8.5 mmol) in tetrahydrofuran (20 ml) and the resulting mixture stirred at ambient temperature for 15 min. Water (15 ml) was added and the organic phase 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 chromatography; elution with light petroleum/ethyl acetate (1:1) provided the *trimethylsilyl ether* (161) (0.65 g, 62%) as cream needles, mp 112-113°. (Found: 247.1385. $C_{14}H_{21}NOSi$ requires 247.1392.) ν_{max} (nujol mull): 3300 (C≡CH); 3275 (NH); 1600, 1500cm^{-1} (C=C Ar). ^{1}H nmr: δ 0.23, s, $Si(CH_3)_3$; 1.55, s, 2xCH_3; 2.34, s, C≡CH; 3.25, br s (exchanges with D_2O), NH; 6.71, d, J 8.8 Hz, 2xArH; 6.88, d, J 8.8 Hz, 2xArH. Mass spectrum *m/z* 247 (M, 60%); 232 (75); 180 (70); 160 (25); 108 (25); 73 (100).

General procedure for the synthesis of 2,2-dimethyl-1,2-dihydroquinolines

A stirred mixture of the N-substituted aniline (11 mmol) and cuprous chloride (250 mg) in toluene (10 ml) was refluxed under an atmosphere of nitrogen for 0.5-2 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*.

By this method the following compounds were prepared:

2,2,6-Trimethyl-1,2-dihydroquinoline[14, 80] *(70)*

(0.84 g, 56%) as an orange oil. ν_{max} (neat film): 3400 (NH); 1630 (C=C); 1600, 1505 cm^{-1} (C=C Ar). ^1H nmr: δ 1.28, s, 2xCH_3; 2.19, s, ArCH_3; 3.53, br s (exchanges with D_2O), NH; 5.46, d, J 9.7 Hz, C=CH; 6.22, d, J 9.7 Hz, C=CH; 6.33, d, J 7.9 Hz, 1xArH; 6.71, d, J 1.6 Hz, 1xArH; 6.77, dd, J 1.6, 7.9 Hz, 1xArH. Mass spectrum *m/z* 173 (M, 50%); 158 (100); 143 (12).

6-Methoxy-2,2-dimethyl-1,2-dihydroquinoline (163)

(0.81 g, 41%) as a yellow oil, bp 60°/0.03mm. (Found: 189.1150. $C_{12}H_{15}NO$ requires 189.1154.) ^1H nmr: δ 1.25, s, 2xCH_3; 2.25, br s (exchanges with D_2O), NH; 3.70, s, OCH_3; 5.45, d, J 9.1 Hz, C=CH; 6.20, d, J 9.1 Hz, C=CH; 6.35-6.60, m, 3xArH. Mass spectrum *m/z* 189 (M, 20%); 174 (100); 159 (15); 131 (40).

6-Bromo-2,2-dimethyl-1,2-dihydroquinoline (164)

(0.19 g, 43%) as orange prisms, mp 59-61°. (Found: 237.0146. $C_{11}H_{12}BrN$ requires 237.0153.) ^1H nmr: δ 1.29, s, 2xCH_3; 3.50, br s (exchanges with D_2O), NH; 5.49, d, J 9.7 Hz, C=CH; 6.18, d, J 9.7 Hz, C=CH; 6.28, d, J 8.3 Hz, 1xArH; 6.9-7.1, m, 2xArH. Mass spectrum *m/z* 237/239 (M, 15%); 222/224 (100); 143 (50).

2,2-Dimethyl-6-trimethylsilyloxy-1,2-dihydroquinoline (171)

(0.35 g, 54%) as an unstable orange oil. (Found: 247.1385. $C_{14}H_{21}NOSi$ requires 247.1392.) ^1H nmr: δ 0.22, s, $Si(CH_3)_3$; 1.28, s, $2xCH_3$; 3.50, br s (exchanges with D_2O), NH; 5.50, d, J 9.6 Hz, C=CH; 6.20, d, J 9.6 Hz, C=CH; 6.31, d, J 8.3 Hz, 1xArH; 6.43, d, J 2.7 Hz, 1xArH; 6.49, dd, J 2.7, 8.3 Hz, 1xArH. Mass spectrum *m/z* 247 (M, 15%); 232 (100); 160 (25); 73 (10).

N-(2,2-Dimethyl-1,2-dihydro-6-quinolyl)acetamide (167)

(0.39 g, 78%) as an orange oil. (Found: 216.1252. $C_{13}H_{15}N_2O$ requires 216.1263.) ^1H nmr: δ 1.24, s, $2xCH_3$; 2.02, s, $COCH_3$; 3.50, br s (exchanges with D_2O), NH amine; 5.48, d, J 9.8 Hz, C=CH; 6.15, d, J 9.8 Hz, C=CH; 6.33, d, J 8.2 Hz, 1xArH; 6.87-7.05, m, 2xArH; 7.98, br s (exchanges with D_2O), NH amide. Mass spectrum *m/z* 216 (M, 15%); 201 (100); 160 (10); 159 (15).

2,2-Dimethyl-6-trimethylsilyl-1,2-dihydroquinoline (168)

(48 mg, 30%) as an unstable orange oil. ^1H nmr: δ 0.20, s, $Si(CH_3)_3$; 1.30, s, $2xCH_3$; 3.70, br s (exchanges with D_2O), NH; 5.45, d, J 9.7 Hz, C=CH; 6.26, d, J 9.5 Hz, 1xArH; 6.39, d, J 9.7 Hz, C=CH; 7.07, m, 2xArH. Mass spectrum *m/z* 231 (M, 1%); 216 (2); 178 (3); 158 (20); 144 (100).

Also obtained from the same reaction was *2,2-dimethyl-1,2-dihydroquinoline* (172) (34 mg, 21%) as an orange oil. (Found: 159.1043. $C_{11}H_{13}N$ requires 159.1048.) ν_{max} (CH_2Cl_2 film): 3375 (NH); 1600, 1500 (C=C Ar); 1540cm^{-1} (C=C). ^1H nmr: δ 1.30, s, $2xCH_3$; 3.64, br s (exchanges with D_2O), NH; 5.46, d, J 9.6 Hz, C=CH; 6.26, d, J 9.6 Hz, C=CH; 6.40, d, J 7.9 Hz, 1xArH; 6.57, t, J 7.5 Hz, 1xArH;

6.87, d, J 7.5 Hz, 1xArH; 6.95, t, J 7.9 Hz, 1xArH. Mass spectrum *m/z* 159 (M, 15%); 145 (15); 144 (100); 143 (10); 128 (5).

Ethyl 2-(2,2-dimethyl-1,2-dihydro-6-quinolyl)acetate (169)

(0.54 g, 57%) as an unstable orange oil. ν_{max} ($CDCl_3$ film): 3375 (NH); 1720 (C=O); 1630 (C=C); 1600, 1495 (C=C Ar); 1250 (C-O); 1020 cm^{-1} (C-O). ^1H nmr: δ 1.24, t, J 7.1 Hz, CH_3; 1.29, s, 2xCH_3; 3.43, s, CH_2; 3.64, br s (exchanges with D_2O), NH; 4.12, q, J 7.1 Hz, OCH_2; 5.46, d, J 9.7 Hz, C=CH; 6.23, d, J 9.7 Hz, C=CH; 6.36, d, J 8.0 Hz, 1xArH; 6.80, d, J 1.9 Hz, 1xArH; 6.87, dd, J 1.9, 8.0 Hz, 1xArH. Mass spectrum *m/z* 246 (M+H, 80%); 245 (M, 20); 244 (M-H, 35); 230 (100); 202 (35); 172 (65); 157 (45).

6-Iodo-2,2-dimethyl-1,2-dihydroquinoline (170)

(0.52 g, 40%) as a light-sensitive orange oil. (Found: 285.0024. $C_{11}H_{12}IN$ requires 285.0016.) ν_{max} (CH_2Cl_2 film): 3390 (NH); 1595, 1490 (C=C Ar); 1550 cm^{-1} (C=C). ^1H nmr: δ 1.29, s, 2xCH_3; 3.66, br s (exchanges with D_2O), NH; 5.46, d, J 9.8 Hz, C=CH; 6.15, d, J 9.8 Hz, C=CH; 6.19, d, J 8.3 Hz, 1xArH; 7.15, dd, J 2.0, 8.3 Hz, 1xArH; 7.19, d, J 2.0 Hz, 1xArH. Mass spectrum *m/z* 285 (M, 22%); 270 (100); 144 (90); 114 (10).

Attempted preparation of 6-amino-2,2-dimethyl-1,2-dihydroquinoline (165)

A stirred mixture of the N-substituted aniline (108) (0.10 g, 0.58 mmol) and cuprous chloride (10 mg) in toluene (2 ml) was refluxed under an atmosphere of nitrogen for 2 h. The rection mixture was cooled and water (5 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. Tlc and ^1H nmr analysis of the residue indicated an extremely complex mixture of products that did not include the desired dihydroquinoline (133).

2-n-Butyl-2-methoxymethyl-6-methyl-1,2-dihydroquinoline (176)

A mixture of the N-substituted aniline (152) (0.68 g, 2.8 mmol) and cuprous chloride (200 mg) in toluene (6 ml) was refluxed under an atmosphere of nitrogen for 30 min. 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 chromatography; elution with light petroleum/ethyl acetate (90:10) gave the *dihydroquinoline* (176) (0.14 g, 21%) as a highly unstable orange oil. ^1H nmr: δ 0.95, t, J 7.3 Hz, CH_3; 1.2-1.6, m, 3xCH_2; 2.24, s, ArCH_3; 3.15, d, J 8.7 Hz, 1H of OCH_2; 3.31, s, OCH_3; 3.40, d, J 8.7 Hz, 1H of OCH_2; 5.28, d, J 8.9 Hz, C=CH; 6.32, d, J 8.9 Hz, C=CH; 6.65, d, J 1.8 Hz, 1xArH; 6.74, dd, J 1.8, 9.6 Hz, 1xArH; 6.90, d, J 9.6 Hz, 1xArH; [NH not visible]. Mass spectrum *m/z* 246 (M+H, 15%); 245 (M, 10); 244 (M-H, 10).

On standing, the dihydroquinoline (176) converted to the *quinoline* (182), which was also isolated from the above reaction (0.16 g, 24%) as an orange oil. (Found: 199.1355. $C_{14}H_{17}N$ requires 199.1361.) ν_{max} (neat film): 1695 (C=N); 1605, 1500 (C=C Ar); 1555 cm^{-1} (C=C). ^1H nmr: δ 0.95, t, J 7.3 Hz, CH_3; 1.35-1.50, m, CH_2; 1.65-1.85, m, CH_2; 2.50, s, ArCH_3; 2.90-3.00, m, CH_2; 7.24, d, J 8.4 Hz, 1xArH; 7.49, m, 2xArH; 7.94, m, 2xArH. Mass spectrum *m/z* 200 (M+H, 5%); 199 (M, 5); 198 (M-H, 5); 184 (10); 170 (25); 157 (100).

1-Trifluoroacetyl-2-n-butyl-2-methoxymethyl-6-methyl-1,2-dihydroquinoline (177)

A stirred mixture of the N-substituted aniline (152) (0.57 g, 2.3 mmol) and cuprous chloride (200 mg) in toluene (10 ml) was refluxed under an atmosphere of nitrogen for 30 min. The reaction mixture was cooled and trifluoroacetic anhydride (0.49 ml, 3.5 mmol) was added under an atmosphere of nitrogen. The resulting mixture was stirred under an atmosphere of nitrogen at ambient temperature for 1 h. Water (15 ml) was added and the organic phase 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 chromatography; elution with light petroleum/ethyl acetate (85:15) afforded the *N-trifluoroacetyl dihydroquinoline* (177) (0.49 g, 63%) as an orange oil. (Found: 341.1588. $C_{18}H_{22}F_3NO_2$ requires 341.1603.) ν_{max} (neat film): 1690 (C=O); 1600, 1500 (C=C Ar); 1570cm^{-1} (C=C). ^{1}H nmr: δ 0.81, t, J 6.9 Hz, CH_3; 1.2-1.6, m, 3xCH_2; 2.31, s, ArCH_3; 3.31, s, OCH_3; 3.70, d, J 9.4 Hz, 1H of OCH_2; 4.23, d, J 9.4 Hz, 1H of OCH_2; 5.81, d, J 9.8 Hz, C=CH; 6.49, d, J 9.8 Hz, C=CH; 6.75, d, J 8.0 Hz, 1xArH; 7.14, br s (not exchangeable with D_2O), 1xArH; 7.30, m, 1xArH. Mass spectrum *m/z* 342 (M+H, 40%); 310 (40); 297 (75); 296 (100); 283 (15).

1-Trifluoroacetyl-2-n-butyl-6-methoxy-2-methoxymethyl-1,2-dihydro-quinoline (178)

A stirred mixture of the N-substituted aniline (153) (20 mg, 0.08 mmol) and cuprous chloride (10 mg) in toluene (3 ml) was refluxed under an atmosphere of nitrogen for 30 min. The reaction mixture was cooled and trifluoroacetic anhydride (16 μl, 0.1 mmol) was added under an atmosphere of nitrogen. The resulting mixture was stirred under an atmosphere of nitrogen at ambient

temperature for 1.5 h. Water (5 ml) was added and the organic phase 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 chromatography; elution with light petroleum/ethyl acetate (80:20) gave the *N-trifluoroacetyl dihydroquinoline* (178) (12 mg, 60%) as an orange oil. ν_{max} (CH_2Cl_2 film): 1690 (C=O); 1605, 1510 (C=C Ar); 1550 cm^{-1} (C=C). ^1H nmr: δ 0.93, t, J 6.9 Hz, CH_3; 1.20-1.55, m, 2xCH_2; 1.70-1.80, m, CH_2; 3.42, s, OCH_3; 3.68, d, J 9.6 Hz, 1H of OCH_2; 3.80, s, OCH_3; 4.23, d, J 9.6 Hz, 1H of OCH_2; 5.88, d, J 9.4 Hz, C=CH; 6.50, d, J 9.4 Hz, C=CH; 6.83, d, J 8.9 Hz, 1xArH; 7.30-7.55, m, 2xArH. Mass spectrum *m/z* 358 (M+H, 5%); 326 (15); 312 (55); 219 (45); 173 (100); 158 (40).

Attempted cyclization of dialkyne (148)

A mixture of the dialkyne (148) (85 mg, 0.35 mmol) and cuprous chloride (10 mg) in toluene (2 ml) was refluxed under an atmosphere of nitrogen for 5 h. The reaction mixture was cooled and water (5 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. ^1H nmr of the crude reaction product indicated an extremely complex mixture which did not show any signals in the olefinic region that could be attributed to either (173) or (174).

Attempted cyclization of N-methyl compound (150)

A mixture of the N-methyl compound (150) (50 mg, 0.29 mmol) and cuprous chloride (10 mg) in toluene (2 ml) was refluxed under an atmosphere of nitrogen for 75 min. The reaction mixture was cooled and water (3 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 chromatography; elution with light petroleum/ethyl acetate (85:15) provided a product that corresponded by ^1H nmr spectroscopy to the starting material (150).

Attempted cyclization of N-propargyl aniline (154)

A stirred mixture of the N-substituted aniline (154) (50 mg, 0.17 mmol) and cuprous chloride (10 mg) in toluene (1 ml) was refluxed under an atmosphere of nitrogen for 48 h. The reaction mixture was cooled and water (5 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 chromatography; elution with light petroleum/ethyl acetate (75:25) provided a product which corresponded by ^1H nmr to the starting N-substituted aniline (154).

Chapter 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 dihydroquinoline (1.53 mmol) in dry dichloromethane (10 ml) and pyridine (0.5 ml) at 0°. The reaction was stirred at ambient temperature for 30min-1 h, then quenched by the slow addition of water (10 ml). The organic phase was separated, washed with 10% hydrochloric acid (3x15 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-trifluoroacetyl dihydroquinolines.*

By this method, the following compounds were prepared:

1-Trifluoroacetyl-2,2,6-trimethyl-1,2-dihydroquinoline (75)

(1.24 g, 75%) as an orange oil. (Found: 269.1011. $C_{14}H_{15}F_3NO$ requires 269.1027.) ν_{max} ($CDCl_3$ film): 1685 (C=O); 1630 (C=C); 1600, 1505 cm^{-1} (C=C Ar). ^1H nmr: δ 1.54, s, 2xCH_3; 2.32, s, ArCH_3; 5.73, d, J 9.7 Hz, C=CH; 6.35, d, J 9.7 Hz, C=CH; 6.76, d, J 8.0 Hz, 1xArH; 6.91, d, J 1.5 Hz, 1xArH; 6.96, dd, J 1.5, 8.0 Hz, 1xArH. Mass spectrum *m/z* 269 (M, 5%); 254 (64); 172 (15); 157 (83); 156 (39); 115 (34); 69 (100).

1-Trifluoroacetyl-6-methoxy-2,2-dimethyl-1,2-dihydroquinoline (183)

(0.19 g, 43%) as an orange oil. (Found (M+H): 286.1061. $C_{14}H_{15}F_3NO_2$ requires 286.1055.) ^{1}H nmr: δ 1.55, s, 2xCH_3; 3.81, s, OCH_3; 5.78, d, J 9.7 Hz, C=CH; 6.35, d, J 9.7 Hz, C=CH; 6.68, m, 2xArH; 6.82, d, J 8.4 Hz, 1xArH. Mass spectrum *m/z* 286 (M+H, 20%); 272 (100); 173 (55); 158 (15); 130 (15).

6-Bromo-1-trifluoroacetyl-2,2-dimethyl-1,2-dihydroquinoline (184)

(0.23 g, 86%) as an orange oil. (Found: 332.9965. $C_{13}H_{11}BrF_3NO$ requires 332.9976.) ^{1}H nmr: δ 1.55, s, 2xCH_3; 5.81, d, J 9.7 Hz, C=CH; 6.33, d, J 9.7 Hz, C=CH; 6.74, d, J 8.4 Hz, 1xArH; 7.2-7.3, m, 2xArH. Mass spectrum *m/z* 333/335 (M, 100); 221/223 (40); 170 (15).

N-(2,2-Dimethyl-1-trifluoroacetyl-1,2-dihydro-6-quinolyl)acetamide (186)

(60 mg, 51%) as orange needles, mp 157-159°. (Found: 312.1092. $C_{15}H_{15}F_3N_2O_2$ requires 312.1086.) ^{1}H nmr: δ 1.54, s, 2xCH_3; 2.18, s, COCH_3; 5.77, d, J 9.7 Hz, C=CH; 6.34, d, J 9.7 Hz, C=CH; 6.81, d, J 8.5 Hz, 1xArH; 7.20, dd, J 2.3, 8.5 Hz, 1xArH; 7.51, d, J 2.3 Hz, 1xArH; 7.92, br s (exchanges with D_2O), NH. Mass spectrum *m/z* 312 (M, 15%); 298 (100); 255 (15); 158 (50).

1-Trifluoroacetyl-6-hydroxy-2,2-dimethyl-1,2-dihydroquinoline (185)

(0.33 g, 86%) as pale orange needles, mp 117-120°. (Found: 271.0810. $C_{13}H_{12}F_3NO_2$ requires 271.0820.) ^{1}H nmr: δ 1.55, s, 2xCH_3; 5.33, br s (exchanges with D_2O), OH; 5.78, d, J 9.7 Hz, C=CH; 6.33, d, J 9.7 Hz, C=CH; 6.64, m, 2xArH;

6.78, d, J 8.6 Hz, 1xArH. Mass spectrum *m/z* 271 (M, 25%); 256 (100); 159 (50); 130 (15); 69 (25).

1-Trifluoroacetyl-2,2-dimethyl-1,2-dihydroquinoline (187)

(0.32 g, 67%) as a pale orange oil. (Found: 255.0865. $C_{13}H_{12}F_3NO$ requires 255.0871.) ν_{max} (neat film): 1695 (C=O); 1490, 1590 (C=C Ar); 1510 cm^{-1} (C=C). ^1H nmr: δ 1.56, s, 2xCH_3; 5.76, d, J 9.7 Hz, C=CH; 6.40, d, J 9.7 Hz, C=CH; 6.87, d, J 7.3 Hz, 1xArH; 7.10, m, 1xArH; 7.18, m, 2xArH. Mass spectrum *m/z* 255 (M, 15%); 240 (100); 170 (15); 143 (35).

(Also obtained from the attempted trifluoroacetylation of the trimethylsilyl substituted dihydroquinoline (136).)

Ethyl 2-(2,2-dimethyl-1-trifluoroacetyl-1,2-dihydro-6-quinolyl)acetate (188)

(0.54 g, 72%) as a yellow oil. (Found: 341.1227. $C_{17}H_{18}F_3NO_3$ requires 341.1239.) ν_{max} ($CDCl_3$ film): 1720 (C=O ester); 1685 (C=O amide); 1640 (C=C); 1595, 1490 cm^{-1} (C=C Ar). ^1H nmr: δ 1.27, t, J 7.1 Hz, CH_3; 1.55, s, 2xCH_3; 3.58, s, CH_2; 4.17, q, J 7.1 Hz, OCH_2; 5.76, d, J 9.7 Hz, C=CH; 6.37, d, J 9.7 Hz, C=CH; 6.82, d, J 8.0 Hz, 1xArH; 7.08, m, 2xArH. Mass spectrum *m/z* 341 (M, 10%); 326 (100); 202 (40); 156 (60).

1-Trifluoroacetyl-6-iodo-2,2-dimethyl-1,2-dihydroquinoline (189)

(0.21 g, 75%) as a light-sensitive yellow oil. (Found: 380.9821. $C_{13}H_{11}F_3INO$ requires 380.9838.) ν_{max} ($CDCl_3$ film): 1700 (C=O amide); 1605, 1495 (C=C Ar); 1560 cm^{-1} (C=C). ^1H nmr: δ 1.55, s, 2xCH_3; 5.79, d, J 9.7 Hz, C=CH; 6.32, d, J 9.7

Hz, C=CH; 6.61, d, J 8.3 Hz, 1xArH; 7.42, d, J 2.0 Hz, 1xArH; 7.48, dd, J 2.0, 8.3 Hz, 1xArH. Mass spectrum *m/z* 381 (M, 15%); 366 (100); 269 (12); 240 (35); 170 (22).

General procedure for the preparation of 3,4-dichlorotetrahydroquinolines:

A 2.4M solution of chlorine in carbon tetrachloride (0.83 mmol) was added dropwise under an atmosphere of nitrogen to a stirred solution of the N-trifluoroacetyl 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 *in vacuo* and the residue purified by flash chromatography; elution with light petroleum/ethyl acetate gave the unstable *3,4-dichloro compounds.*

By this method, the following compounds were prepared:

3,4-Dichloro-1-trifluoroacetyl-6-methoxy-2,2-dimethyl-1,2,3,4-tetrahydro-quinoline (199)

(0.21 g, 88%) as an unstable yellow oil. (Found: 355.0343. $C_{14}H_{14}Cl_2F_3NO_2$ requires 355.0354.) ^1H nmr: δ 1.51, s, CH_3; 1.81, s, CH_3; 3.84, s, OCH_3; 4.47, d, J 4.5 Hz, CHCl; 5.19, d, J 4.5 Hz, CHCl; 6.88, dd, J 2.8, 8.8 Hz, 1xArH; 6.94, d, J 8.8 Hz, 1xArH; 7.04, d, J 2.8 Hz, 1xArH. Mass spectrum *m/z* 355/357/359 (M, 100%); 322/324/326 (70); 280/282 (100); 272 (50); 230 (55); 188 (55).

3,4-Dichloro-1-trifluoroacetyl-2,2-dimethyl-1,2,3,4-tetrahydroquinoline (203)

(0.34 g, 83%) as an unstable yellow oil. (Found: 325.0245. $C_{13}H_{12}Cl_2F_3NO$ requires 325.0248.) ^1H nmr: δ 1.55, s, CH_3; 1.80, s, CH_3; 4.48, d, J 4.5 Hz, CHCl; 5.27, d, J 4.5 Hz, CHCl; 6.98, m, 1xArH; 7.36, m, 2xArH; 7.54, dd, J 3.7, 5.8 Hz, 1xArH. Mass spectrum *m/z* 325/327/329 (M, 25%); 290/292 (100); 253 (20); 239 (40).

6-Bromo-3,4-dichloro-1-trifluoroacetyl-2,2-dimethyl-1,2,3,4-tetrahydro-quinoline (200)

(0.25 g, 90%) as an unstable pale yellow oil. (Found: 402.9334. $C_{13}H_{11}BrCl_2F_3NO$ requires 402.9353.) ^1H nmr: δ 1.56, s, CH_3; 1.77, s, CH_3; 4.44, d, J 4.4 Hz, CHCl; 5.21, d, J 4.4 Hz, CHCl; 6.85, d, J 8.3 Hz, 1xArH; 7.48, dd, J 2.1, 8.3 Hz, 1xArH; 6.68, d, J 2.1 Hz, 1xArH. Mass spectrum *m/z* 403/405/407 (M, 40%); 368/370/372 (100); 247 (60).

N-(3,4-Dichloro-2,2-dimethyl-1-trifluoroacetyl-1,2,3,4-tetrahydro-6-quinolyl)acetamide (202)

(50 mg, 75%) as unstable pale yellow needles, mp 145-147°. (Found: 382.0476. $C_{15}H_{15}Cl_2F_3N_2O_2$ requires 382.0463.) ^1H nmr: δ 1.53, s, CH_3; 1.79, s, CH_3; 2.20, s, $COCH_3$; 4.46, d, J 4.4 Hz, CHCl; 5.20, d, J 4.4 Hz, CHCl; 6.93, d, J 8.7 Hz, 1xArH; 7.52, dd, J 2.2, 8.7 Hz, 1xArH; 7.84, d, J 2.2 Hz, 1xArH; 8.14, br s (exchanges with D_2O), NH. Mass spectrum *m/z* 382/384/386 (M, 100%); 347/349 (75); 312 (100); 305/307 (90); 297 (100).

3,4-Dichloro-1-trifluoroacetyl-6-hydroxy-2,2-dimethyl-1,2,3,4-tetrahydro-quinoline (201)

(0.13 g, 100%) as unstable pale yellow needles, mp 100-102°. ^{1}H nmr: δ 1.53, s, CH_3; 1.81, s, CH_3; 4.45, d, J 4.6 Hz, CHCl; 5.16, d, J 4.6 Hz, CHCl; 6.25, br s (exchanges with D_2O), OH; 6.84, dd, J 2.6, 8.6 Hz, 1xArH; 6.90, d, J 8.6 Hz, 1xArH; 7.03, d, J 2.6 Hz, 1xArH. Mass spectrum *m/z* 341/343/345 (M, 100%); 306 (75); 266 (30); 264 (90); 216 (60); 174 (90).

Problems with the stability of (201) prevented a satisfactory microanalysis or accurate mass from being obtained; however, the next compound in the series, (190), was obtained analytically pure.

Ethyl 2-(3,4-dichloro-2,2-dimethyl-1,2,3,4-tetrahydro-6-quinolyl)acetate (204)

(0.60 g, 92%) as an unstable yellow oil. (Found: 411.0596. $C_{17}H_{18}Cl_2F_3NO_3$ requires 411.0616.) ν_{max} ($CDCl_3$ film): 1720 (C=O ester); 1695 (C=O amide); 1595, 1495 (C=C Ar); 740 cm^{-1} (C-Cl). ^{1}H nmr: δ 1.27, t, J 7.0 Hz, CH_3; 1.55, s, CH_3; 1.78, s, CH_3; 3.65, s, CH_2; 4.18, q, J 7.0 Hz, OCH_2; 4.45, d, J 4.5 Hz, CHCl; 5.25, d, J 4.5 Hz, CHCl; 6.93, d, J 8.0 Hz, 1xArH; 7.28, dd, J 1.8, 8.0 Hz, 1xArH; 7.48, d, J 1.8 Hz, 1xArH. Mass spectrum *m/z* 411/413/415 (M, 35%); 376/378 (100); 340 (25); 326 (55); 260 (40).

3,4-Dichloro-1-trifluoroacetyl-6-iodo-2,2-dimethyl-1,2,3,4-tetrahydroquinoline (205)

(0.17 g, 68%) as unstable white prisms, mp 75-77°. ν_{max} ($CDCl_3$ film): 1680 (C=O); 1600, 1505 (C=C Ar); 745 cm^{-1} (C-Cl). ^1H nmr: δ 1.56, s, CH_3; 1.77, s, CH_3; 4.43, d, J 4.4 Hz, CHCl; 5.19, d, J 4.4 Hz, CHCl; 6.70, d, J 8.4 Hz, 1xArH; 7.66, dd, J 1.9, 8.4 Hz, 1xArH; 7.86, d, J 1.9 Hz, 1xArH. Mass spectrum *m/z* 451/453/455 (M, 60%); 416/418 (55); 368 (22); 290 (26); 247 (22); 69 (100).

Methyl 3,4-dichloro-2,2-dimethyl-1-trifluoroacetyl-1,2,3,4-tetrahydroquinoline-6-carboxylate (206)

(63 mg, 80%) as unstable yellow prisms, mp 104-106°. (Found: 383.0303. $C_{15}H_{14}Cl_2F_3NO_3$ requires 383.0303.) ν_{max} ($CDCl_3$ film): 1780 (C=O ester); 1700 (C=O amide); 1605, 1500 (C=C Ar); 740 cm^{-1} (C-Cl). ^1H nmr: δ 1.59, s, CH_3; 1.77, s, CH_3; 3.95, s, OCH_3; 4.48, d, J 4.3 Hz, CHCl; 5.32, d, J 4.3 Hz, CHCl; 6.99, d, J 8.3 Hz, 1xArH; 8.02, dd, J 1.9, 8.3 Hz, 1xArH; 8.23, d, J 1.9 Hz, 1xArH. Mass spectrum *m/z* 383/385/387 (M, 22%); 348/350 (100); 312 (13); 298 (20); 258 (16); 216 (15).

2-n-*Butyl-3,4-dichloro-1-trifluoroacetyl-2-methoxymethyl-6-methyl-1,2,3,4-tetrahydroquinoline (207)*

(0.27 g, 57%) as an unstable, viscous yellow oil. (Found: 411.1040. $C_{18}H_{22}Cl_2F_3NO_2$ requires 411.0980.) ^1H nmr: δ 0.79, t, J 7.1 Hz, CH_3; 1.1-1.7, m, 3xCH_2; 2.40, s, ArCH_3; 3.36, s, OCH_3; 3.92, d, J 10.3 Hz, 1H of OCH_2; 4.26, d, J 10.3 Hz, 1H of OCH_2; 4.39, d, J 6.2 Hz, CHCl; 5.60, d, J 6.2 Hz, CHCl; 6.87, d, J 7.8 Hz,

1xArH; 7.13, dd, J 1.4, 7.8 Hz, 1xArH; 7.48, d, J 1.4 Hz, 1xArH. Mass spectrum *m/z* 411/413/415 (M, 15%); 365/368/369 (100); 330/332 (10); 296 (50); 294 (20).

1-Acetyl-3,4-dibromo-2,2,6-trimethyl-1,2,3,4-tetrahydroquinoline (215)

Bromine (0.44 g, 2.7 mmol) was added dropwise to a stirred solution of the dihydroquinoline (214) (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 *in vacuo* and the residue purified by flash chromatography; elution with light petroleum/ethyl acetate (60:40) provided the *dibromo compound* (215) (0.94 g, 91%) as a highly unstable orange oil. ^{1}H nmr: δ 1.37, s, CH_3; 1.91, s, CH_3; 2.10, s, $ArCH_3$; 2.36, s, $COCH_3$; 4.89, d, J 3.9 Hz, CHBr; 5.55, d, J 3.9 Hz, CHBr; 6.90, d, J 8.2 Hz, 1xArH; 7.11, dd, J 1.7, 8.2 Hz, 1xArH; 7.23, d, J 1.7 Hz, 1xArH. Mass spectrum *m/z* 373/375/377 (M, 2%); 314/316/318 (25); 294/296 (10); 236/238 (15); 200 (20); 158 (100).

3,4-Dichloro-2,2,6-trimethyl-1,2,3,4-tetrahydroquinoline (213)

A 2.4M solution of chlorine in carbon tetrachloride (0.18 ml, 0.43 mmol) was added dropwise to a stirred solution of the dihydroquinoline (70) (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 neutralized with 10% sodium hydroxide solution and extracted with dichloromethane (3x10 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* (213) (33 mg, 47%) as highly unstable white prisms, mp 107-109°. ^{1}H nmr: δ 1.24, s, CH_3; 1.39, s, CH_3; 2.25, s, $ArCH_3$; 2.60, br s (exchanges with

D_2O), NH; 3.98, d, J 9.2 Hz, CHCl; 4.76, d, J 9.2 Hz, CHCl; 6.49, d, J 8.1 Hz, 1xArH; 6.92, dd, J 1.5, 8.1 Hz, 1xArH; 7.25, d, J 1.5 Hz, 1xArH. Mass spectrum *m/z* 243/245/247 (M, 1%); 208/210 (25); 192/194 (100).

General procedure for the synthesis of 3-chlorotetrahydroquinolines:

Sodium cyanoborohydride (1.75 mmol) was added to a solution of freshly dried zinc chloride[22] (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 (3x15 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:

3-Chloro-1-trifluoroacetyl-2,2-dimethyl-1,2,3,4-tetrahydroquinoline (219)

(0.20 g, 66%) as colourless prisms, mp 40-42°. (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%) ^1H nmr: δ 1.65, s, CH_3; 1.68, s, CH_3; 3.12, dd, J 6.3, 15.5 Hz, 1H of CH_2; 3.25, dd, J 3.6, 15.5 Hz, 1H of CH_2; 4.19, dd, J 3.6, 6.3 Hz, CHCl; 6.99, m, 1xArH; 7.24, m, 1xArH. Mass spectrum *m/z* 291/293 (M, 20%); 256 (5); 240 (10); 214 (100); 202 (25); 158 (15).

3-Chloro-1-trifluoroacetyl-6-methoxy-2,2-dimethyl-1,2,3,4-tetrahydro-quinoline (216)

(0.14 g, 78%) as a pale yellow oil. (Found: 321.0749. $C_{14}H_{15}ClF_3NO_2$ requires 321.0743.) ^{1}H nmr: δ 1.66, s, 2xCH_3; 3.05, dd, J 6.3, 15.3 Hz, 1H of CH_2; 3.19, dd, J 3.6, 15.3 Hz, 1H of CH_2; 3.81, s, OCH_3; 4.17, dd, J 3.6, 6.3 Hz, CHCl; 6.75, m, 2xArH; 6.93, d, J 8.8 Hz, 1xArH. Mass spectrum *m/z* 321/323 (M, 60%); 286 (15); 270 (10); 244 (100); 232 (25); 188 (15).

6-Bromo-3-chloro-1-trifluoroacetyl-2,2-dimethyl-1,2,3,4-tetrahydroquinoline (217)

(40 mg, 20%) as white needles, mp 78-80°. (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%) ^{1}H nmr: δ 1.63, s, CH_3; 1.67, s, CH_3; 3.09, dd, J 5.8, 15.8 Hz, 1H of CH_2; 3.24, dd, J 3.5, 15.8 Hz, 1H of CH_2; 4.21, dd, J 3.5, 5.8 Hz, CHCl; 6.86, dd, J 0.8, 8.9 Hz, 1xArH; 7.37, m, 2xArH. Mass spectrum *m/z* 369/371/373 (M, 50%); 292/294 (75); 279/281 (25); 213 (100).

N-(3-Chloro-2,2-dimethyl-1-trifluoroacetyl-1,2,3,4-tetrahydro-6-quinolyl)acetamide (218)

(30 mg, 55%) as pale yellow prisms, mp 146-148°. (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%) ^{1}H nmr: δ 1.63, s, CH_3; 1.67, s, CH_3; 2.19, s, $COCH_3$; 3.07, dd, J 5.9, 15.6 Hz, 1H of CH_2; 3.21, dd, J 3.5, 15.6 Hz, 1H of CH_2; 4.19, dd, J 3.5, 5.9 Hz, CHCl; 6.93, d, J 8.6 Hz, 1xArH; 7.26, dd, J 2.3, 8.6 Hz, 1xArH; 7.65, d, J 2.3 Hz, 1xArH; 7.78, br s (exchanges with D_2O), NH. Mass spectrum *m/z* 348/350 (M, 35%); 313 (5); 271 (60); 254 (45); 223 (100).

3-Chloro-1-trifluoroacetyl-6-hydroxy-2,2-dimethyl-1,2,3,4-tetrahydroquinoline (190)

(80 mg, 88%) as a white powder, mp 118-119°. (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%) ^{1}H nmr: δ 1.65, s, CH_3; 1.67, s, CH_3; 3.04, dd, J 6.2, 15.4 Hz, 1H of CH_2; 3.17, dd, J 3.5, 15.4 Hz, 1H of CH_2; 4.18, dd, J 3.5, 6.2 Hz, CHCl; 5.91, br s (exchanges with D_2O), OH; 6.70, d, J 2.7 Hz, 1xArH; 6.73, dd, J 2.7, 8.3 Hz, 1xArH; 6.89, d, J 8.3 Hz, 1xArH. Mass spectrum *m/z* 307/309 (M, 30%); 272 (5); 230 (100); 218 (25); 174 (12).

Ethyl 2-(3-chloro-2,2-dimethyl-1,2,3,4-tetrahydro-6-quinolyl)acetate (220)

(0.42 g, 76%) as a viscous, pale yellow oil. (Found: 377.0994. $C_{17}H_{19}ClF_3NO_3$ requires 377.1005.) ν_{max} ($CDCl_3$ film): 1720 (C=O ester); 1685 (C=O amide); 1595, 1495 cm^{-1} (C=C Ar). ^{1}H nmr: δ 1.26, t, J 7.2 Hz, CH_3; 1.64, s, CH_3; 1.67, s, CH_3; 3.11, dd, J 3.7, 15.6 Hz, 1H of CH_2; 3.23, dd, J 6.4, 15.6 Hz, 1H of CH_2; 3.61, s, $ArCH_2$; 4.17, m, CHCl and OCH_2; 6.94, br s (not exchangeable with D_2O), 1xArH; 7.15, m, 2xArH. Mass spectrum *m/z* 378/380 (M+H, 35%); 342 (7); 300 (20); 288 (25); 226 (100).

3-Chloro-1-trifluoroacetyl-6-iodo-2,2-dimethyl-1,2,3,4-tetrahydroquinoline (221)

(50 mg, 33%) as a viscous, pale yellow oil. (Found: 416.9585. $C_{13}H_{12}ClF_3INO$ requires: 416.9606.) ν_{max} ($CDCl_3$ film): 1700 (C=O); 1605, 1500 (C=C Ar); 740 cm^{-1} (C-Cl). ^{1}H nmr: δ 1.62, s, CH_3; 1.67, s, CH_3; 3.07, dd, J 5.8, 15.8 Hz, 1H of CH_2; 3.22, dd, J 3.6, 15.8 Hz, 1H of CH_2; 4.19, dd, J 3.6, 5.8 Hz, CHCl; 6.72, d, J 8.8 Hz, 1xArH; 7.24, m, 1xArH; 7.56, br s (not exchangeable with D_2O), 1xArH. Mass

spectrum *m/z* 417/419 (M, 40%); 382 (5); 340 (40); 291 (20); 258 (25); 214 (85); 69 (100).

Methyl 3-chloro-2,2-dimethyl-1-trifluoroacetyl-1,2,3,4-tetrahydroquinoline-6-carboxylate (222)

(16 mg, 34%) as a colourless oil. (Found: 349.0692. $C_{15}H_{15}ClF_3NO_3$ requires 349.0693.) ν_{max} (CH_2Cl_2 film): 1720 (C=O ester); 1705 (C=O amide); 1610, 1510 (C=C Ar); 1255 cm^{-1} (C-O). ^1H nmr: δ 1.63, s, CH_3; 1.69, s, CH_3; 3.13, dd, J 5.6, 16.0 Hz, 1H of CH_2; 3.19, dd, J 3.7, 16.0 Hz, 1H of CH_2; 3.93, s, OCH_3; 4.24, dd, J 3.7, 5.6 Hz, CHCl; 7.02, d, J 7.9 Hz, 1xArH; 7.92, m, 2xArH. Mass spectrum *m/z* 349/351 (M, 38%); 272 (100); 260 (49); 240 (20); 228 (42).

2-n-Butyl-3-chloro-1-trifluoroacetyl-2-methoxymethyl-6-methyl-1,2,3,4-tetrahydroquinoline (223)

(0.30 g, 91%) as a viscous, pale yellow oil. (Found: 377.1376. $C_{18}H_{25}ClF_3NO_2$ requires 377.1369.) ^1H nmr: δ 0.80, t, J 7.2 Hz, CH_3; 1.0-1.6, m, 3xCH_2; 2.24, s, ArCH_3; 3.06, dd, J 4.3, 16.0 Hz, 1H of CH_2; 3.35, s, OCH_3; 3.53, dd, J 7.2, 16.0 Hz, 1H of CH_2; 3.93, d, J 10.2 Hz, 1H of OCH_2; 4.22, d, J 10.2 Hz, 1H of OCH_2; 4.28, dd, J 4.3, 7.2 Hz, CHCl; 6.8-7.0, m, 3xArH. Mass spectrum *m/z* 377/379 (M, 25%); 332/334 (100); 296 (30).

3-Chloro-1-trifluoroacetyl-6-trifluoromethanesulphonate-2,2-dimethyl-1,2,3,4-tetrahydroquinoline (191)

N-Phenyltriflimide (27 mg, 0.07 mmol) was added to a stirred solution of the monochloro compound (190) (23 mg, 0.07 mol) and triethylamine (0.5 ml) in dichloromethane (2 ml) cooled to 0°. The reaction mixture was stirred at room temperature under an atmosphere of nitrogen for 3 h, washed with 5% hydrochloric acid (2x10 ml), dried and the solvent removed. The residue was purified by flash chromatography; elution with light petroleum/ethyl acetate (75:25) gave the *triflate* (191) (28 mg, 98%) as a colourless oil. ν_{max} ($CDCl_3$ film): 1695 (C=O amide); 1590, 1485 (C=C Ar); 1420 (SO_2); 1200 cm^{-1} (SO_2). ^1H nmr: δ 1.65, s, CH_3; 1.69, s, CH_3; 3.16, dd, J 5.4, 15.9 Hz, 1H of CH_2; 3.31, dd, J 3.6, 15.9 Hz, 1H of CH_2; 4.26, dd, J 3.6, 5.4 Hz, CHCl; 7.06, d, J 9.2 Hz, 1xArH; 7.18, m, 2xArH. Mass spectrum *m/z* 439/441 (M, 10%); 404 (5); 306 (25); 225 (30); 92 (100).

Attempted CO insertion on triflate (191)

A mixture of the triflate (191) (35 mg, 0.08 mmol), triethylamine (22 µl, 0.16 mmol), palladium *tetrakis*(triphenylphosphine) (0) (3 mg, 2.38 µmol), methanol (66 µl, 1.59 mmol) and dimethylformamide (2 ml) was purged with carbon monoxide for 5 min and then stirred at 60° under an atmosphere of carbon monoxide (balloon) for 2.5 h. The reaction mixture was cooled, diluted with brine (5 ml) and extracted with ether (3x10 ml). The combined organic extracts were washed with 5% hydrochloric acid (15 ml) and brine (2x10 ml), dried and the solvent removed. The residue was purified by flash chromatography; elution with light petroleum/ethyl acetate (80:20) provided a product whose ^1H nmr spectrum corresponded to that of the unreacted triflate (191).

Methyl 2,2-dimethyl-1-trifluoroacetyl-1,2-dihydroquinoline-6-carboxylate (193)

A mixture of the iodo-substituted dihydroquinoline (189) (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, 66 µmol) was added and the resulting mixture stirred at 100° under an atmosphere of carbon monoxide (balloon) 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 (3x15 ml) and brine (2x15 ml), dried and the solvent removed. The residue was purified by flash chromatography; elution with light petroleum/ethyl acetate (80:20) provided the *ester* (193) (16 mg, 39%) as colourless needles, mp 92-94°. (Found: 313.0934. $C_{15}H_{14}F_3NO_3$ requires 313.0926.) ν_{max} (CH_2Cl_2 film): 1780 (C=O ester); 1690 (C=O amide); 1600, 1500 (C=C Ar); 1580 (C=C); 1260 cm^{-1} (C-O). ^1H nmr: δ 1.57, s, 2xCH_3; 3.92, s, OCH_3; 5.81, d, J 9.7 Hz, C=CH; 6.45, d, J 9.7 Hz, C=CH; 6.88, d, J 8.2 Hz, 1xArH; 7.78, d, J 2.0 Hz, 1xArH; 7.85, dd, J 2.0, 8.2 Hz, 1xArH. Mass spectrum *m/z* 313 (M, 5%); 298 (100); 170 (31); 157 (16); 115 (22).

Further elution gave *methyl-2,2-dimethyl-1,2-dihydroquinoline-6-carboxylate* (194) (10 mg, 25%) as unstable tan prisms, mp 85-87°. (Found: 217.1092. $C_{13}H_{15}NO_2$ requires 217.1103.) ν_{max} ($CDCl_3$ film): 3400 (NH); 1705 (C=O); 1640 (C=C); 1600, 1500 cm^{-1} (C=C Ar). ^1H nmr: δ 1.33, s, CH_3; 3.83, s, OCH_3; 4.13, br s (exchanges with D_2O), NH; 5.46, dd, J 1.9, 9.8 Hz, C=CH; 6.26, d, J 9.8 Hz, C=CH; 6.34, d, J 8.4 Hz, 1xArH; 7.55, d, J 1.9 Hz, 1xArH; 7.65, dd, J 1.9, 8.4 Hz, 1xArH. Mass spectrum *m/z* 217 (M, 8%); 202 (100); 143 (20); 115 (10).

Attempted Heck coupling of (189) with methyl methacrylate

A mixture of the iodide (189) (100 mg, 0.26 mmol), methyl methacrylate (35 µl, 0.33 mmol), triphenylphosphine (82 mg, 0.31 mmol) and triethylamine (3 ml) was purged with nitrogen for 10 min. Palladium acetate (12 mg, 52 µmol) was added and the resulting mixture refluxed under an atmosphere of nitrogen for 5 h. The reaction mixture was cooled, water (10 ml) added and the resultant mixture extracted with ether (3x10 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) provided the starting iodo compound (189).

A reaction using conditions identical to those above, except that methyl methacrylate was replaced with methyl acrylate, was also carried out, and gave the same result as that reported above.

Attempted Heck coupling of (189) with methyl acrylate

A solution of the iodide (189) (92 mg, 0.24 mmol), methyl acrylate (43 µl, 0.48 mmol) and triphenylphosphine (0.13 g, 0.48 mmol) in triethylamine (0.67 ml, 4.8 mmol) and dry dimethylformamide (2 ml) was purged with nitrogen for 10 min. Palladium *tetrakis*(triphenylphosphine) (0) (28 mg, 24 µmol) was added and the resulting mixture stirred at 105° under an atmosphere of nitrogen for 24 h. Workup as above provided a crude reaction mixture in which only the starting iodide (189) and a trace amount of the unsubstituted dihydroquinoline (187) could be detected by ^{1}H nmr.

Attempted hydrolyses of the trifluoroacetamide (223)

1. Using acid catalysis

A mixture of the amide (223) (20 mg, 0.05 mmol), concentrated sulphuric acid (1 drop) and ethanol was refluxed under an atmosphere of nitrogen for 48 h. Tlc of the crude reaction mixture indicated the presence of starting material only.

2. Using base catalysis

A solution of the amide (223) (50 mg, 0.13 mmol) in 10% potassium hydroxide in methanol (2 ml) was refluxed under an atmosphere of nitrogen for 1 h. Tlc of the crude reaction mixture revealed it to be a highly complex mixture of at least five new products.

2-n-butyl-3-chloro-2-methoxymethyl-6-methyl-1,2,3,4-tetrahydroquinoline (225)

A solution of the trifluoroacetamide (223) (50 mg, 0.13 mmol) in 10% potassium hydroxide in methanol (2 ml) was stirred at room temperature for 2.5 h. Water (5 ml) was added and the mixture extracted with dichloromethane (4x10 ml). The combined organic extracts were dried and the solvent removed. The residue was purified by flash chromatography; elution with light petroleum/ethyl acetate (90:10) provided the *amine* (225) (28 mg, 75%) as colourless prisms, mp 65-67°. (Found: 281.1559. $C_{16}H_{24}ClNO$ requires 281.1546.) ν_{max} ($CDCl_3$ film): 3400 (NH); 1605, 1500 cm^{-1} (C=C Ar). ^1H nmr: δ 0.89, t, J 9.1 Hz, CH_3; 1.25-1.36, m, 2xCH_2; 1.54-1.73, m, CH_2; 2.21, s, ArCH_3; 3.00, dd, J 6.6, 17.1 Hz, 1H of CH_2; 3.27, dd, J 5.2, 17.1 Hz, 1H of CH_2;

3.35, s, OCH_3; 3.47, d, J 8.9 Hz, 1H of OCH_2; 3.52, d, J 8.9 Hz, 1H of OCH_2; 3.90, br s (exchanges with D_2O), NH; 4.32, dd, J 5.2, 6.6 Hz, CHCl; 6.47, d, J 8.0 Hz, 1xArH; 6.79, s, 1xArH; 6.83, d, J 8.0 Hz, 1xArH. Mass spectrum *m/z* 281/283 (M, 11%); 236/238 (84); 200 (41); 170 (19); 157 (100).

1-Acetyl-3-chloro-2,2,6-trimethyl-1,2,3,4-tetrahydroquinolin-4-ol (227)

A solution of chlorine in carbon tetrachloride (2.4M; 0.15 ml, 0.35 mmol) was added dropwise to a solution of the dihydroquinoline (214) (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 (3x10 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* (227) (60 mg, 96%) as cream prisms, mp 139-141°. (Found: 267.1018. $C_{14}H_{18}ClNO_2$ requires 267.1026.) ν_{max} ($CDCl_3$ film): 3600-3550 (OH); 1650 (C=O); 1600, 1505 cm^{-1} (C=C Ar). ^1H nmr: δ 1.68, s, CH_3; 1.69, s, CH_3; 2.11, s, $COCH_3$; 2.37, s, $ArCH_3$; 2.84, br s (exchanges with D_2O), OH; 3.67, d, J 9.5 Hz, CHCl; 4.71, dd, J 3.0, 9.5 Hz, C<u>H</u>OH; 6.84, d, J 8.1 Hz, 1xArH; 7.07, dd, J 1.8, 8.1 Hz, 1xArH; 7.39, d, J 1.8 Hz, 1xArH. Mass spectrum *m/z* 267/269 (M, 44%); 225/227 (60); 210/212 (100); 198 (46).

3-Chloro-1-trifluoroacetyl-2,2,6-trimethyl-1,2,3,4-tetrahydroquinolin-4-ol (228)

A solution of chlorine in carbon tetrachloride (2.4M; 0.23 ml, 0.36 mmol) was added dropwise to a stirred solution of the dihydroquinoline (75) (0.1 g, 0.37 mmol) in tetrahydrofuran (2 ml) and water (2 ml) and the resulting mixture stirred vigorously for 72 h. Water (5 ml) was added and the mixture extracted with dichloromethane (3x10 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) gave the *chlorohydrin* (228) (43 mg, 36%) as a pale yellow gum. (Found: 321.0733. $C_{14}H_{15}ClF_3NO_2$ requires 321.0743.) ν_{max} ($CDCl_3$ film): 3595 (OH); 1690 (C=O); 1595, 1500 cm^{-1} (C=C Ar). ^1H nmr: δ 1.67, s, CH_3; 1.68, s, CH_3; 2.39, s, $ArCH_3$; 2.85, br s (exchanges with D_2O), OH; 3.69, d, J 9.2 Hz, CHCl; 4.74, d, J 9.2 Hz, C<u>H</u>OH; 6.89, d, J 8.4 Hz, 1xArH; 7.11, dd, J 1.6, 8.4 Hz, 1xArH; 7.43, d, J 1.6 Hz, 1xArH. Mass spectrum *m/z* 321/323 (M, 100%); 244 (54); 216 (45); 203 (63); 162 (86).

Also obtained from the same reaction was *1-trifluoroacetyl-3,4-dichloro-1,2,3,4-tetrahydroquinoline* (229) (59 mg, 47%) as a pale yellow oil. (Found: 339.0402. $C_{14}H_{14}Cl_2F_3NO$ requires 339.0404.) ν_{max} ($CDCl_3$ film): 1700 (C=O); 1590, 1500 cm^{-1} (C=C Ar). ^1H nmr: δ 1.52, s, CH_3; 1.79, s, CH_3; 2.38, s, $ArCH_3$; 4.47, d, J 4.4 Hz, CHCl; 5.22, d, J 4.4 Hz, CHCl; 6.87, d, J 8.3 Hz, 1xArH; 7.14, dd, J 1.5, 8.3 Hz, 1xArH; 7.33, d, J 1.5 Hz, 1xArH. Mass spectrum *m/z* 339/341/343 (M, 32%); 304/306 (77); 262 (45); 214 (34); 172 (50); 69 (100).

3,4-Epoxy-1-trifluoroacetyl-2,2,6-trimethyl-1,2,3,4-tetrahydroquinoline (231)

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 (75) (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 (3x15 ml) and water (2x15 ml), dried and the solvent removed. The residue was purified by flash chromatography; elution with light petroleum/ethyl acetate (70:30) afforded the *epoxide* (231) (0.39 g, 74%) as a pale orange oil. (Found: 285.0980. $C_{14}H_{14}F_3NO_2$ requires 285.0977.) ν_{max} ($CDCl_3$ film): 1700 (C=O); 1595, 1500 cm^{-1} (C=C Ar). ^1H nmr: δ 1.21, s, CH_3; 1.88, s, CH_3; 2.37, s, $ArCH_3$; 3.41, d, J 4.2 Hz, CH; 3.86, d, J 4.2 Hz, CH; 6.77, d, 8.1 Hz, 1xArH; 7.12, dd, J 1.8, 8.1 Hz, 1xArH; 7.26, d, J 1.8 Hz, 1xArH. Mass spectrum *m/z* 285 (M, 46%); 214 (100); 145 (29); 144 (28); 69 (48).

1-Trifluoroacetyl-2,2,6-trimethyl-1,2,3,4-tetrahydroquinolin-3-ol (232)

A solution of the epoxide (231) (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* (232) (0.27 g, 69%) as a colourless, unstable oil. (Found: 287.1123. $C_{14}H_{16}F_3NO_2$ requires 287.1133.) ν_{max} ($CDCl_3$ film): 3600 (OH); 1695 (C=O); 1600, 1500 (C=C Ar); 1300 cm^{-1} (OH bend). ^1H nmr: δ 1.43, d, J 7.8 Hz (exchanges with D_2O), OH; 1.56, s, CH_3; 1.59, s, CH_3; 2.35, s, $ArCH_3$; 2.82, dd, J 5.5, 14.4 Hz, 1H of CH_2; 2.94, dd, J 2.4, 14.4 Hz, 1H of CH_2; 3.89, m, C<u>H</u>OH; 6.91, d, J 7.9 Hz, 1xArH; 7.04, m, 2xArH. Mass spectrum *m/z* 287 (M, 84%); 271 (48); 217 (25); 216 (30); 190 (35); 158 (100).

1-Trifluoroacetyl-2,2,6-trimethyl-1,2,3,4-tetrahydro-3-quinolone (233)

Jones reagent was added dropwise to a solution of the alcohol (232) (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 (3x10 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* (233) (7.3 mg, 74%) as a pale yellow oil. (Found: 285.0970. $C_{14}H_{14}F_3NO_2$ requires 285.0977.) ν_{max} ($CDCl_3$ film): 1730 (C=O ketone); 1695 (C=O amide); 1600, 1505 cm^{-1} (C=C Ar). ^1H nmr (acquired at 0° - see Appendix, page 190): δ 1.34, s, CH_3; 1.79, s, CH_3; 2.31, s, $ArCH_3$; 3.36, d, J 13.8 Hz, 1H of CH_2; 3.87, d, J 13.8 Hz, 1H of CH_2; 7.01, d, J 8.0 Hz, 1xArH; 7.11, m, 2xArH. Mass spectrum *m/z* 285 (M, 30%); 257 (60); 242 (58); 188 (50); 160 (90); 145 (100).

2,2,6-Trimethyl-1,2,3,4-tetrahydro-3-quinolyl trifluoroacetate (235)

The alcohol (232) (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 diethylazodicarboxylate (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* (235) (78 mg, 78%) as an unstable pale yellow oil. ν_{max} ($CDCl_3$) film): 3400 (NH); 1780 (C=O ester); 1605, 1500 cm^{-1} (C=C Ar). ^1H nmr: δ 1.20, s, CH_3; 1.22, s, CH_3; 2.22, s, $ArCH_3$; 2.86, dd, J 7.4, 16.9 Hz, 1H of CH_2; 3.15, dd, J 5.5, 16.9 Hz, 1H of CH_2; 3.56, br s (exchanges with D_2O), NH; 5.10, dd, J 5.5, 7.4 Hz, CHOR; 6.46, d, J 8.1 Hz,

1xArH; 6.81, s, 1xArH; 6.84, d, J 8.1 Hz, 1xArH. Mass spectrum *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 (235) as the sole product.

2,2,6-Trimethyl-1,2,3,4-tetrahydroquinolin-3-ol (236)

A 10% aqueous solution of potassium bicarbonate (2.5 ml, 2.4 mmol) was added dropwise to a solution of the trifluoroacetate (235) (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 (3x10 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* (236) (40 mg, 78%) as cream prisms, mp 73-74°C. (Found: 191.1314. $C_{12}H_{17}NO$ requires 191.1310.) ν_{max} ($CDCl_3$ film): 3500 (OH); 3370 (NH); 1610, 1500 cm^{-1} (C=C Ar). ^1H nmr: δ 1.11, s, CH_3; 1.20, s, CH_3; 2.18, br s (exchanges with D_2O), OH; 2.21, s, $ArCH_3$; 2.71, dd, J 4.4, 17.0 Hz, 1H of CH_2; 2.99, dd, J 4.4, 17.0 Hz, 1H of CH_2; 3.46, br s (exchanges with D_2O), NH; 3.63, t, J 4.4 Hz, C<u>H</u>OH; 6.43, d, J 8.7 Hz, 1xArH; 6.81, m, 2xArH. Mass spectrum *m/z* 191 (M, 69%); 176 (100); 158 (31); 146 (34); 132 (36).

3-Chloro-2,2,6-trimethyl-1,2,3,4-tetrahydroquinoline (237)

1. Attempted preparation using sodium cyanoborohydride and dichloro compound (213)

Sodium cyanoborohydride (24 mg, 0.37 mmol) was added to a solution of freshly dried zinc chloride[22] (26 mg, 0.19 mmol) in dry ether (5 ml) and the mixture stirred at room temperature under an atmosphere of nitrogen for 20 min. A solution of the dichlorotetrahydroquinoline (213) (23 mg, 0.09 mmol) in dry ether (2 ml) was added under an atmosphere of nitrogen and the resulting mixture stirred at ambient temperature for 96 h. The reaction was quenched with saturated sodium bicarbonate solution (5 ml), the organic phase separated, washed with water (5 ml) and brine (2x5 ml), dried and the solvent removed. The residue was purified by flash chromatography; elution with light petroleum/ethyl acetate (85:15) afforded the starting dichloro compound (213).

2. Attempted preparation using $SOCl_2$ and alcohol (236)

A solution of thionyl chloride (31 µl, 0.42 mmol) in dichloromethane (1 ml) was added dropwise under an atmosphere of nitrogen to a stirred solution of the alcohol (236) (40 mg, 0.21 mmol) and the resulting solution heated to 40° for 4.5 h. The reaction mixture was cooled and the solvent and excess thionyl chloride removed *in vacuo*. Tlc and ^1H nmr of the residue indicated an extremely complex product mixture in which the chloro compound (237) could not be detected.

3. *Using tetrabutylammonium chloride and the trifluoroacetate (235)*

A mixture of the trifluoroacetate (235) (20 mg, 70 μmol), tetrabutylammonium chloride (15 mg, 0.14 mmol) and tetrahydrofuran (5 ml) was refluxed for 24 h. The reaction mixture was cooled, diluted with dichloromethane (5 ml), washed with water (2x10 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 (235) and the *3-chloro compound* (237) (6.5 mg). Spectroscopic data for (237) was determined by subtraction. ^{1}H nmr: δ 1.25, s, CH_3; 1.30, s, CH_3; 2.21, s, $ArCH_3$; 3.03, dd, J 8.4, 16.9 Hz, 1H of CH_2; 3.23, dd, J 5.4, 16.9 Hz, 1H of CH_2; 3.60, br s (exchanges with D_2O), NH; 4.08, dd, J 5.4, 8.4 Hz, CHCl; 6.45, d, J 8.0 Hz, 1xArH; 6.83, m, 2xArH. Mass spectrum *m/z* 209/211 (M, 29%); 194 (1); 174 (1); 158 (2).

Chapter 4

Note: because the compounds synthesized in this Chapter were unstable, microanalyses were not able to be obtained. However, where possible, all new compounds were characterized by accurate mass.

N,N'-bis-(2-*Methylbut*-3-*yn*-2-*yl*)-m-*phenylenediamine* (243)

A solution of the chloroalkyne (61) (1.19 g, 11.6 mmol) in tetrahydrofuran (1 ml) was added slowly to a stirred mixture of *m*-phenylenediamine (0.50 g, 4.6 mmol), cuprous chloride (50 mg), copper bronze powder (50 mg) and triethylamine (1.61 ml, 11.6 mmol) in tetrahydrofuran (10 ml) and water (0.5 ml) and the resulting mixture stirred at room temperature under an atmosphere of nitrogen for 1 h. Water (15 ml) was added and the organic phase 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 chromatography; elution with light petroleum/ethyl acetate (60:40) gave the *dialkyne* (243) (0.34 g, 31%) as an unstable orange oil. (Found: 240.1615. $C_{16}H_{20}N_2$ requires 240.1626.) ^{1}H nmr: δ 1.61, s, 4xCH_3; 2.36, s, 2xC≡CH; 3.61, br s (exchanges with D_2O), 2xNH; 6.32, dd, J 2.3, 8.1 Hz, 2xArH; 6.72, t, J 2.3 Hz, 1xArH; 6.98, t, J 8.1 Hz, 1xArH. Mass spectrum *m*/z 240 (M, 95%); 225 (100); 210 (25); 209 (30); 173 (90); 159 (75).

Attempted cyclization of m-*substituted dialkyne* (243)

A mixture of the dialkyne (243) (0.33 g, 1.9 mmol) and cuprous chloride (50 mg) in toluene (3 ml) was refluxed under an atmosphere of nitrogen for 20 min. The reaction mixture was cooled, water (5 ml) added and the organic

phase separated and combined with the dichloromethane extracts of the aqueous phase. The combined organic extracts were dried and the solvent removed. ^1H nmr of the residue was very poorly resolved and did not show any signals that could be attributed to a double bond.

N-(2-Methylbut-3-yn-2-yl)-3-methylaniline (239)

A solution of the chloroalkyne (61) (0.72 g, 7.0 mmol) in tetrahydrofuran (1 ml) was added slowly to a stirred mixture of *m*-toluidine (0.50 g, 4.7 mmol), cuprous chloride (50 mg), copper bronze powder (50 mg) and triethylamine (0.97 ml, 7.0 mmol) in tetrahydrofuran (5 ml) and water (0.5 ml) and the resulting mixture stirred at room temperature under an atmosphere of nitrogen for 30 min. Water (10 ml) was added and the organic phase 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 chromatography; elution with light petroleum/ethyl acetate (85:15) provided the *N-substituted aniline* (239) (0.67 g, 83%) as a red oil. (Found: 173.1203. $C_{12}H_{15}N$ requires 173.1204.) ν_{max} ($CDCl_3$ film): 3400 (NH); 3300 (C≡CH); 1605, 1510 cm^{-1} (C=C Ar). ^1H nmr: δ 1.60, s, 2xCH_3; 2.29, s, ArCH_3; 2.36, s, C≡CH; 3.61, br s (exchanges with D_2O), NH; 6.62, d, J 7.7 Hz, 1xArH; 6.73, br s (not exchangeable with D_2O), 1xArH; 6.78, dd, J 2.3, 8.3 Hz, 1xArH; 7.09, t, J 7.7 Hz, 1xArH. Mass spectrum *m/z* 173 (M, 65%); 158 (100); 143 (10); 107 (44).

2,2,5- and 2,2,7-Trimethyl-1,2-dihydroquinoline (240) and (241)

A mixture of the N-substituted aniline (239) (0.40 g, 2.5 mmol) and cuprous chloride (100 mg) in toluene (4 ml) was refluxed under an atmosphere of nitrogen for 20 min. The reaction mixture was cooled, water (5 ml) added and the organic phase 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 chromatography; elution with light petroleum/ethyl acetate (85:15) gave an inseparable 1:1 mixture of the *2,2,5-dihydroquinoline* (241) and the *2,2,7-dihydroquinoline* (240) (0.28 g, 70%) as a yellow oil. (Found: 173.1196. $C_{12}H_{15}N$ requires 173.1204.) ν_{max} ($CDCl_3$ film): 3400 (NH); 1640 (C=C); 1620 (C=C); 1600, 1500 cm^{-1} (C=C Ar). ^1H nmr: δ 1.29, s, 4xCH_3 (2xCH_3 for each isomer); 2.20, s, ArCH_3; 2.24, s, ArCH_3; 3.60, br s (exchanges with D_2O), 2xNH; 5.40, d, J 9.7 Hz, C=CH; 5.50, d, J 9.9 Hz, C=CH; 6.23, br s (not exchangeable with D_2O), 1xArH; 6.25, m, 1xArH; 6.43, m, 2xArH and C=CH; 6.77, d, J 7.5 Hz, 1xArH; 6.85, t, J 7.7 Hz, 1xArH. Mass spectrum *m/z* 173 (M, 12%); 158 (100).

N-(2-Methylbut-3-yn-2-yl)-2-methylaniline (248)

A mixture of *o*-toluidine (0.60 g, 5.6 mmol), chloroalkyne (61) (0.86 g, 8.4 mmol), cuprous chloride (50 mg), copper bronze (50 mg) and triethylamine (1.17 ml, 8.4 mmol) in tetrahydrofuran (10 ml) and water (0.5 ml) was stirred under an atmosphere of nitrogen for 30 min. Water (10 ml) was added and the organic phase 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 chromatography; elution with light petroleum/ethyl acetate (85:15) provided the *N-propargyl aniline* (248) (0.27 g, 28%) as an orange oil. (Found: 173.1197. $C_{12}H_{15}N$ requires

173.1204.) ν_{max} ($CDCl_3$ film): 3415 (NH); 3300 (C≡CH); 1600, 1505 cm^{-1} (C=C Ar). ^1H nmr: δ 1.65, s, 2xCH_3; 2.13, s, ArCH_3; 2.37, s, C≡CH; 3.53, br s (exchanges with D_2O), NH; 6.71, dt, J 0.9, 7.3 Hz, 1xArH; 7.10, m, 2xArH; 7.29, dd, J 0.9, 8.2 Hz, 1xArH. Mass spectrum *m/z* 173 (M, 41%); 158 (100); 143 (25); 107 (85); 106 (77).

2,2,8-Trimethyl-1,2-dihydroquinoline (250)

A mixture of the N-propargyl aniline (248) (0.27 g, 1.6 mmol) and cuprous chloride (50 mg) in toluene (5 ml) was refluxed under an atmosphere of nitrogen for 1.5 h. The reaction mixture was cooled, water (5 ml) added and the organic phase 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 chromatography; elution with light petroleum/ethyl acetate (85:15) provided the *dihydroquinoline* (250) (0.14 g, 52%) as a yellow oil. (Found: 173.1191. $C_{12}H_{15}N$ requires 173.1204.) ν_{max} ($CDCl_3$ film): 3415 (NH); 1630 (C=C); 1600, 1505 cm^{-1} (C=C Ar). ^1H nmr: δ 1.32, s, 2xCH_3; 2.07, s, ArCH_3; 3.50, br s (exchanges with D_2O), NH; 5.45, d, J 9.7 Hz, C=CH; 6.26, d, J 9.7 Hz, C=CH; 6.51, t, J 7.5 Hz, 1xArH; 6.78, d, J 7.5 Hz, 1xArH; 6.86, d, J 7.5 Hz, 1xArH. Mass spectrum *m/z* 173 (M, 2%); 158 (100); 157 (24).

N-(2-Methylbut-3-yn-2-yl)-2-methoxyaniline (249)

A mixture of *o*-anisidine (0.50 g, 4.1 mmol), chloroalkyne (61) (0.63 g, 6.1 mmol), cuprous chloride (50 mg), copper bronze (50 mg) and triethylamine (0.85 ml, 6.1 mmol) in tetrahydrofuran (10 ml) and water (0.5 ml) was stirred under an atmosphere of nitrogen for 30 min. Water (10 ml) was added and

the organic phase 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 chromatography; elution with light petroleum/ethyl acetate (85:15) gave the *N-propargyl aniline* (249) (0.35 g, 46%) as a pale orange oil. (Found: 189.1158. $C_{12}H_{15}NO$ requires 189.1154.) ν_{max} ($CDCl_3$ film): 3420 (NH); 3300 (C≡CH); 1600, 1505 (C=C Ar); 1225 cm^{-1} (C-O). ^1H nmr: δ 1.64, s, 2xCH_3; 2.36, s, C≡CH; 3.83, s, OCH_3; 4.35, br s (exchanges with D_2O), NH; 6.74, m, 2xArH; 6.88, dt, J 1.5, 7.9 Hz, 1xArH; 7.27, dd, J 1.5, 7.9 Hz, 1xArH. Mass spectrum *m/z* 189 (M, 43%); 174 (100); 159 (12); 144 (23); 123 (54).

8-Methoxy-2,2-dimethyl-1,2-dihydroquinoline (251)

A mixture of the N-propargyl aniline (249) (0.35 g, 1.9 mmol) and cuprous chloride (50 mg) in toluene (5 ml) was refluxed under an atmosphere of nitrogen for 1.5 h. The reaction mixture was cooled, water (5 ml) added and the organic phase 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 chromatography; elution with light petroleum/ethyl acetate (85:15) provided the *dihydroquinoline* (251) (0.22 g, 63%) as a pale yellow oil. (Found: 189.1150. $C_{12}H_{15}NO$ requires 189.1154.) ν_{max} ($CDCl_3$ film): 3400 (NH); 1630 (C=C); 1600, 1500 cm^{-1} (C=C Ar). ^1H nmr: δ 1.31, s, 2xCH_3; 3.81, s, OCH_3; 4.17, br s (exchanges with D_2O), NH; 5.45, d, J 9.7 Hz, C=CH; 6.26, d, J 9.7 Hz, C=CH; 6.58, m, 3xArH. Mass spectrum *m/z* 189 (M, 9%); 174 (100); 159 (46); 131 (14).

N-Propargyl-p-toluidine (253)

Propargyl bromide (0.37 ml, 4.2 mmol) was added dropwise under an atmosphere of nitrogen to a stirred mixture of *p*-toluidine (0.45 g, 4.2 mmol) and potassium carbonate (0.87 g, 6.3 mmol) in dichloromethane (10 ml) and the resulting mixture stirred at room temperature under an atmosphere of nitrogen for 24 h. Water (10 ml) was added and the organic phase 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 chromatography; elution with light petroleum/ethyl acetate (70:30) provided a yellow solid which was recrystallized from dichloromethane/light petroleum to give the *N-propargyl aniline* (253) (0.15 g, 25%) as colourless needles, mp 46-47°. (Found: 145.0886. $C_{10}H_{11}N$ requires 145.0891.) ν_{max} (CH_2Cl_2 film): 3405 (NH); 3300 (C≡CH); 1605, 1500 cm^{-1} (C=C Ar). ^1H nmr: δ 2.20, t, J 2.4 Hz, C≡CH; 2.25, s, CH_3; 3.74, br s (exchanges with D_2O), NH; 3.91, d, J 2.4 Hz, CH_2; 6.62, d, J 8.5 Hz, 2xArH; 7.03, d, J 8.5 Hz, 2xArH. Mass spectrum *m/z* 145 (M, 100%); 144 (M-H, 55); 130 (52); 106 (50); 91 (24).

Also obtained from the same reaction was the *dialkyne* (254) (20 mg, 3%) as an orange oil. (Found: 183.1042. $C_{13}H_{13}N$ requires 183.1048.) ν_{max} ($CDCl_3$ film): 3300 (C≡CH); 1610, 1505 cm^{-1} (C=C Ar). ^1H nmr: δ 2.24, t, J 2.4 Hz, 2xC≡CH; 2.28, s, CH_3; 4.08, d, J 2.4 Hz, 2xCH_2; 6.89, d, J 8.7 Hz, 2xArH; 7.10, d, J 8.7 Hz, 2xArH. Mass spectrum *m/z* 183 (M, 100%); 168 (24); 167 (30); 144 (33); 143 (29); 142 (28).

6-Methylquinoline (255)

A mixture of the N-propargyl aniline (253) (0.10 g, 0.69 mmol) and cuprous chloride (70 mg, 0.69 mmol) in toluene (5 ml) was refluxed under an atmosphere of nitrogen for 30 min. The reaction mixture was cooled, diluted with dichloromethane (5 ml) and extracted with 10% hydrochloric acid (3x10 ml). The aqueous extracts were combined and ethylenediamine tetraacetic acid (0.25 g, 0.7 mmol) was added with stirring. The resulting mixture was basified to pH 12 with solid sodium hydroxide and extracted with dichloromethane (3x15 ml). The combined organic extracts were dried and the solvent removed. The residue was purified by flash chromatography; elution with light petroleum/ethyl acetate (70:30) gave the *quinoline* (255) (38 mg, 38%) as a light-sensitive orange oil. ν_{max} (CH_2Cl_2 film): 1630 (C=N); 1600, 1500 (C=C Ar); 1575 cm^{-1} (C=C). ^1H nmr: δ 2.52, s, CH_3; 7.34, br s (not exchangeable with D_2O), 1xArH; 7.53, m, 2xArH; 8.03, m, 2xArH; 8.89, m, 1xArH. Mass spectrum *m/z* 143 (M, 100%); 142 (46); 120 (7); 115 (16).

p-*Toluidine-N-benzylidene (256)*

A stirred mixture of *p*-toluidine (1.00 g, 9.4 mmol) and benzaldehyde (0.99 g, 9.4 mmol) was heated at 100° for 30 min. The reaction mixture was cooled, dissolved in dichloromethane (20 ml), dried and the solvent removed. The residue was purified by flash chromatography; elution with light petroleum/ethyl acetate provided the *imine*[67] (256) (1.65 g, 91%) as a colourless oil. ν_{max} (CH_2Cl_2 film): 1630 (C=N); 1600, 1505 (C=C Ar). ^1H nmr: δ 2.36, s, $ArCH_3$; 7.15, m, 4xArH; 7.45, m, 3xArH; 7.88, m, 2xArH; 8.46, s, N=CH. Mass spectrum *m/z* 195 (M, 100%); 194 (M-H, 64); 118 (10); 91 (46); 77 (9).

Attempted preparation of monosubstituted N-propargyl aniline (257) using imine (256)

Butyllithium (2.5M in hexanes; 0.56 ml, 1.41 mmol) was added dropwise under an atmosphere of nitrogen to a stirred solution of trimethylsilylacetylene (0.15 g, 1.54 mmol) in dry tetrahydrofuran (10 ml) cooled to -70° with the resulting mixture stirred at this temperature for 20 min. A solution of the imine (256) (0.25 g, 1.28 mmol) in dry tetrahydrofuran (5 ml) was added dropwise at -70° and the mixture stirred at this temperature for 45 min. The reaction mixture was quenched at -70° by the careful addition of saturated ammonium chloride (15 ml) and the organic phase separated and combined with ethereal extracts of the aqueous phase. The combined organic extracts were dried and the solvent removed. The residue was purified by flash chromatography; elution with light petroleum/ethyl actetate gave the starting imine (256).

3-Butyn-2-yl acetate (259)

Acetyl chloride (0.76 ml, 10.7 mmol) was added dropwise to a stirred solution of 3-butyn-2-ol (0.50 g, 7.1mmol) in pyridine (1 ml) and dichloromethane (2 ml) cooled to 0°. The resulting mixture was allowed to warm to room temperature and stirred at this temperature for 2 h. The mixture was diluted with dichloromethane (5 ml), washed with 10% hydrochloric acid (3x10 ml), dried and the solvent removed. The residue was purified by flash chromatography; elution with light petroleum/ethyl acetate (70:30) provided the *acetate* (259) (0.68 g, 85%) as a colourless oil. ν_{max} ($CDCl_3$ film): 3300 (C≡CH); 1735 (C=O); 1240 cm^{-1} (C-O). ^1H nmr: δ 1.50, d, J 6.7 Hz, CH_3; 2.09, s, $COCH_3$; 2.46, d, J 2.2 Hz, C≡CH; 5.43, dq, J 2.2, 6.7 Hz, OCH. Mass spectrum *m/z* 112 (M, 4%); 97 (8); 69 (23); 43 (100).

Attempted coupling of acetate (259) to p-*toluidine*

1. Using cuprous chloride/triethylamine

A stirred mixture of *p*-toluidine (0.24 g, 2.2 mmol), the acetate (259) (0.25 g, 2.2 mmol), cuprous chloride (50 mg) and triethylamine (0.47 ml, 3.4 mmol) in tetrahydrofuran (10 ml) was refluxed under an atmosphere of nitrogen for 24 h. The reaction mixture was cooled, diluted with water (10 ml) and extracted with dichloromethane (3x10 ml). The combined organic extracts were dried and the solvent removed. The residue was purified by flash chromatography; elution with light petroleum/ethyl acetate (30:70) provided unreacted *p*-toluidine and *acet*-p-*toluidide* (261) (30 mg, 8%) as cream needles, mp 144-145° (lit.[87] 146°). ν_{max} (CH_2Cl_2 film): 3400 (NH); 1690 (C=O); 1600, 1510 cm^{-1} (C=C Ar). ^1H nmr: δ 2.13, s, $COCH_3$; 2.30, s, $ArCH_3$; 7.09, d, J 8.3 Hz, 2xArH; 7.37, d, J 8.3 Hz, 2xArH; 7.69, br s (exchanges with D_2O), NH. Mass spectrum *m/z* 149 (M, 100); 131 (24); 107 (65); 106 (49).

2. Direct S_N2 displacement of acetate group

A mixture of the acetate (259) (50 mg, 0.45 mmol), *p*-toluidine (48 mg, 0.45 mmol), potassium carbonate (92 mg, 0.67 mmol) and tetrahydrofuran (5 ml) was stirred at room temperature under an atmosphere of nitrogen for 24 h. Water (5 ml) was added and the mixture extracted with dichloromethane (3x10 ml). The organic extracts were dried and the solvent removed. ^1H nmr of the residue indicated a mixture of the starting acetate (259), *p*-toluidine and the toluidide (261).

N-(2-Methylbut-3-yn-2-yl)-3-aminoquinoline (264)

A solution of the chloroalkyne (61) (0.44 g, 4.3 mmol) in tetrahydrofuran (1 ml) was added slowly to stirred mixture of 3-aminoquinoline (0.50 g, 3.5 mmol), cuprous chloride (50 mg), copper bronze powder (50 mg) and triethylamine (0.72 ml, 5.2 mmol) in tetrahydrofuran (5 ml) and water (250 µl) and the resulting mixture stirred at room temperature under an atmosphere of nitrogen for 2 h. Water (10 ml) was added and the organic phase 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 chromatography; elution with light petroleum/ethyl acetate (35:65) gave the *coupled product* (264) (0.46 g, 63%) as orange prisms, mp 102-104°. ν_{max} (CH_2Cl_2 film): 3650 (NH); 3300 (C≡CH); 1600, 1505 (C=C Ar); 1550 cm^{-1} (C=N). ^1H nmr: δ 1.69, s, 2xCH_3; 2.44, s, C≡CH; 4.08, br s (exchanges with D_2O), NH; 7.45, m, 2xArH; 7.63, d, J 2.9 Hz, 1xArH; 7.68, m, 1xArH; 7.95, m, 1xArH; 8.48, d, J 2.9 Hz, 1xArH. Mass spectrum *m/z* 210 (M, 55%); 195 (80); 168 (20); 144 (90); 176 (30); 69 (100).

3,3-Dimethyl-3,4-dihydro-4,6-phenanthroline (266)

A mixture of the N-propargyl quinoline (264) (0.10 g, 0.48 mmol) and cuprous chloride (10 mg) in toluene (2 ml) was refluxed under an atmosphere of nitrogen for 2 h. The reaction mixture was cooled, water (5 ml) added and the organic phase 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 chromatography; elution with light petroleum/ethyl acetate (25:75) gave the *cyclized compound* (266) (33 mg, 33%) as an unstable orange oil. ^1H nmr: δ 1.37, s, 2xCH_3; 4.16, br s (exchanges with D_2O), NH; 5.74, dd, J 2.2, 10.0 Hz, C=CH; 6.94, d, J 10.0 Hz, C=CH; 7.42, m,

2xArH; 7.83, d, J 9.3 Hz, 1xArH; 7.92, d, J 8.7 Hz, 1xArH; 8.32, br s (not exchangeable with D_2O), 1xArH.

6-Aminoquinoline (268)

A mixture of 6-nitroquinoline (1.0 g, 5.8 mmol) and 5% palladium on carbon (100 mg) in ethanol (10 ml) was stirred under an atmosphere of hydrogen for 6 h. The mixture was filtered through a small pad of celite and the solvent removed. The residue was purified by flash chromatography; elution with dichloromethane/methanol (95:5) gave the *aminoquinoline* (268) (0.81 g, 98%) as yellow prisms, mp 115-117° (lit.[88] 117-119°). ν_{max} ($CDCl_3$ film): 3475, 3290 (NH_2); 1625 (C=N); 1595, 1505 cm^{-1} (C=C Ar). ^1H nmr: δ 3.99, br s (exchanges with D_2O), NH_2; 6.90, d, J 2.6 Hz, 1xArH; 7.15, dd, J 2.6, 9.0 Hz, 1xArH; 7.26, dd, J 4.2, 8.3 Hz, 1xArH; 7.89, dd, J 1.7, 8.3 Hz, 1xArH; 7.91, d, J 9.0 Hz, 1xArH; 8.65, dd, J 1.7, 4.2 Hz, 1xArH. Mass spectrum *m/z* 145 (M+H, 40%); 144 (M, 100); 117 (25); 89 (10).

N-(2-Methylbut-3-yn-2-yl)-6-aminoquinoline (269)

A solution of the chloroalkyne (61) (0.53 g, 5.2 mmol) in tetrahydrofuran (1 ml) was added slowly to a stirred mixture of 6-aminoquinoline (0.50 g, 3.5 mmol), cuprous chloride (100 mg), copper bronze powder (100 mg) and triethylamine (0.72 ml, 5.2 mmol) in tetrahydrofuran (10 ml) and water (0.5 ml) and the resulting mixture stirred at room temperature under an atmosphere of nitrogen for 3 h. Water (10 ml) was added and the organic phase 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 chromatography; elution with

dichloromethane/ methanol (95:5) provided the *coupled product* (269) (0.20 g, 28%) as an orange oil. (Found: 210.1152. $C_{14}H_{14}N_2$ requires 210.1157.) ν_{max} ($CDCl_3$ film): 3390 (NH); 3300 (C≡CH); 1610, 1505 (C=C Ar); 1540 cm^{-1} (C=N). ^1H nmr: δ 1.67, s, 2xCH_3; 2.44, s, C≡CH; 4.29, br s (exchanges with D_2O), NH; 7.22, m, 3xArH; 7.89, d, J 9.1 Hz, 1xArH; 7.96, dd, J 1.1, 8.3 Hz, 1xArH; 8.60, d, J 3.0 Hz, 1xArH. Mass spectrum *m/z* 211 (M+H, 40%); 196 (100); 144 (55); 116 (15).

3,3-Dimethyl-3,4-dihydro-4,7-phenanthroline (271)

A mixture of the N-propargyl quinoline (269) (0.15 g, 7.4 mmol) and cuprous chloride (50 mg) in toluene (5 ml) was refluxed under an atmosphere of nitrogen for 30 min. The reaction mixture was cooled, water (5 ml) added and the organic phase 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 chromatography; elution with dichloromethane/methanol (95:5) provided the *phenanthroline* (271) (63 mg, 42%) as a yellow oil. (Found: 210.1146. $C_{14}H_{14}N_2$ requires 210.1157.) ν_{max} (CH_2Cl_2 film): 3370 (NH); 1620 (C=N); 1590, 1500 (C=C Ar); 1540 cm^{-1} (C=C). ^1H nmr: δ 1.34, s, 2xCH_3; 4.23, br s (exchanges with D_2O), NH; 5.35, dd, J 2.0, 9.9 Hz, C=CH; 6.87, d, J 9.9 Hz, C=CH; 6.93, d, J 9.0 Hz, 1xArH; 7.25, dd, J 4.2, 8.5 Hz, 1xArH; 7.65, d, J 9.0 Hz, 1xArH; 8.15, d, J 8.5 Hz, 1xArH; 8.58, d, J 4.2 Hz, 1xArH. Mass spectrum *m/z* 211 (M+H, 15%); 196 (100); 195 (20); 86 (35); 84 (60).

N-(2-Methylbut-3-yn-2-yl)-8-amino-6-methoxy-2-methylquinoline (274)

A solution of the chloroalkyne (61) (38 mg, 0.37 mmol) in tetrahydrofuran (1 ml) was added to a mixture of the 8-aminoquinoline (273) (46 mg, 0.25 mmol), cuprous chloride (10 mg), copper bronze powder (10 mg) and triethylamine (51 µl, 0.37 mmol) in tetrahydrofuran (5 ml) and water (100 µl) and the resulting mixture stirred at room temperature under an atmosphere of nitrogen for 1 h. Water (5 ml) was added and the organic phase 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 chromatography; elution with dichloromethane gave the *coupled product* (274) (7.6 mg, 12%) as off-white prisms, mp 110-111°. (Found: 254.1406. $C_{16}H_{18}N_2O$ requires 254.1419.) ^1H nmr: δ 1.77, s, 2xCH_3; 2.41, s, C≡CH; 2.64, s, ArCH_3; 3.89, s, OCH_3; 6.38, d, J 2.5 Hz, 1xArH; 6.43, br s (exchanges with D_2O), NH; 6.95, d, J 2.5 Hz, 1xArH; 7.18, d, J 8.3 Hz, 1xArH; 7.82, d, J 8.3 Hz, 1xArH. Mass spectrum *m/z* 254 (M, 40%); 239 (100); 213 (10); 196 (10); 188 (20).

6-Methoxy-2,9,9-trimethyl-9,10-dihydro-1,10-phenanthroline (275)

A mixture of the N-substituted quinoline (274) (8 mg, 0.03 mmol), cuprous chloride (10 mg) and toluene (2 ml) was refluxed under an atmosphere of nitrogen for 30 min. The reaction mixture was cooled, water (5 ml) added and the organic phase 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 chromatography; elution with dichloromethane gave the *phenanthroline* (275) (2.4 mg, 30%) as a glassy, red-brown solid, mp 78-79° (dec.). (Found: 254.1425. $C_{16}H_{18}N_2O$ requires 254.1425.) ν_{max} ($CDCl_3$ film): 3300 (NH); 1620 (C=N); 1595, 1500 (C=C

Ar); 1550 cm^{-1} (C=C). ^1H nmr: δ 1.41, s, 2xCH_3; 2.64, s, ArCH_3; 3.89, s, OCH_3; 5.48, dd, J 2.2, 9.8 Hz, C=CH; 5.94, br s (exchanges with D_2O), NH; 6.25, s, 1xArH; 6.73, d, J 9.8 Hz, C=CH; 7.10, d, J 8.3 Hz, 1xArH; 7.74, d, J 8.3 Hz, 1xArH. Mass spectrum *m/z* 254 (M, 11%); 239 (100); 224 (36); 213 (48); 196 (23); 170 (32).

Attempted preparation of N-(2-methylbut-3-yn-2-yl)-2-aminoquinoline (263)

A solution of the chloroalkyne (61) (0.44 g, 4.3 mmol) in tetrahydrofuran (1 ml) was added slowly to a mixture of 2-aminoquinoline (0.50 g, 3.4 mmol), cuprous chloride (50 mg), copper bronze powder (50 mg) and triethylamine (0.72 ml, 5.2 mmol) in tetrahydrofuran (5 ml) and water (0.5 ml), whereupon a black precipitate formed. The resulting mixture was stirred at room temperature under an atmosphere of nitrogen for 2.5 h, water (10 ml) was added and the organic phase separated and combined with the dichloromethane extracts of the aqueous phase. Tlc of the residue indicated formation of a copper complex, as evidenced by the significant amount on baseline material, and a ^1H nmr of the residue indicated an extremely complex mixture that did not contain any of the desired coupled product (263).

Attempted preparation of N-(2-methylbut-3-yn-2-yl)-2-aminoanthraquinone (277)

A solution of the chloroalkyne (61) (0.34 g, 3.4 mmol) in tetrahydrofuran (1 ml) was added slowly to a mixture of 2-aminoanthraquinone (0.50 g, 2.2 mmol), cuprous chloride (50 mg), copper bronze powder (50 mg) and triethylamine (0.47 ml, 3.4 mmol) in tetrahydrofuran (10 ml) and water (0.5 ml) and the resulting mixture stirred at room temperature under an

atmosphere of nitrogen for 24 h. Water (10 ml) was added and the organic phase separated and combined with the dichloromethane extracts of the aqueous phase. The combined organic extracts were dried and the solvent removed. Tlc and ^{1}H nmr of the residue indicated the formation of only a trace amount of the desired coupled product (277).

2-Aminoanthracene (278)

A mixture of 2-aminoanthraquinone (0.50 g, 2.2 mmol), zinc powder (0.82 g, 12.6 mmol), 95% ethanol (0.5 ml) and 10% aqueous sodium hydroxide (10 ml) was refluxed for 24 h. The reaction mixture was cooled and the solid material collected, washed with hot water and air-dried. Soxhlet extraction of this solid with acetone gave the crude anthracene, which was crystallized from acetone to give *2-aminoanthracene* (278) (0.20 g, 47%) as lustrous yellow plates, mp 237-238° (lit.[65] 238-239°). ν_{max} ($CDCl_3$ film): 3400 (NH_2); 1605, 1500 cm^{-1} (C=C Ar). ^{1}H nmr: δ 3.92, br s (exchanges with D_2O), NH_2; 6.99, dd, J 2.2, 9.0 Hz, 1xArH; 7.08, d, J 2.2 Hz, 1xArH; 7.38, m, 2xArH; 7.88, m, 3xArH; 8.11, s, 1xArH; 8.28, s, 1xArH. Mass spectrum *m/z* 193 (M, 100%); 165 (36); 139 (8); 96 (18).

N-(2-Methylbut-3-yn-2-yl)-2-aminoanthracene (279)

A solution of the chloroalkyne (61) (0.12 g, 1.2 mmol) in tetrahydrofuran (1 ml) was added slowly to a stirred mixture of 2-aminoanthracene (0.15 g, 0.78 mmol), cuprous chloride (50 mg), copper bronze powder (50 mg) and triethylamine (0.16 ml, 1.2 mmol) in tetrahydrofuran (10 ml) and water (0.5 ml) with the resultant mixture stirred under an atmosphere of nitrogen for 45 min. Water (10 ml) was added and the organic phase 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 chromatography; elution with light petroleum/ethyl acetate (80:20) provided the *coupled product* (279) (40 mg, 22%) as orange needles, mp 85-87°. (Found: 259.1353. $C_{19}H_{17}N$ requires 259.1361.) ν_{max} ($CDCl_3$ film): 3415 (NH); 3300 (C≡CH); 1625, 1510 cm^{-1} (C=C Ar). ^1H nmr: δ 1.70, s, 2xCH_3; 2.45, s, C≡CH; 3.91, br s (exchanges with D_2O), NH; 6.95, dd, J 2.3, 9.0 Hz, 1xArH; 7.35, m, 3xArH; 7.79, d, J 9.0 Hz, 1xArH; 7.88, m, 2xArH; 8.19, s, 1xArH; 8.23, s, 1xArH. Mass spectrum *m/z* 259 (M, 50%); 244 (72); 193 (69); 165 (100); 84 (29).

Naphtho-[2,3-f]-3,3-dimethyl-3,4-dihydroquinoline (281)

A mixture of the coupled product (279) (40 mg, 0.15 mmol) and cuprous chloride (15 mg) in toluene (2 ml) was refluxed under an atmosphere of nitrogen for 45 min. The reaction mixture was cooled, water (5 ml) was added and the organic phase 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 chromatography; elution with light petroleum/ethyl acetate (80:20) gave the *cyclized compound* (281) (22 mg, 55%) as a viscous orange oil. (Found: 259.1360. $C_{19}H_{17}N$ requires 259.1361.) ν_{max} ($CDCl_3$ film): 3435 (NH); 1630, 1540 (C=C Ar); 1555 cm^{-1} (C=C). ^1H nmr: δ 1.36, s, 2xCH_3; 3.92, br s (exchanges with D_2O), NH; 5.54, dd, J 1.1, 9.8 Hz, C=CH; 6.74, d, J 9.0 Hz, 1xArH; 7.13, d, J 9.8 Hz, C=CH; 7.34, m, 2xArH; 7.68, d, J 9.0 Hz, 1xArH; 7.87, t, J 8.1 Hz, 2xArH; 8.18, s, 1xArH; 8.31, s, 1xArH. Mass spectrum *m/z* 259 (M, 11%); 244 (88); 122 (16); 86 (64); 84 (100).

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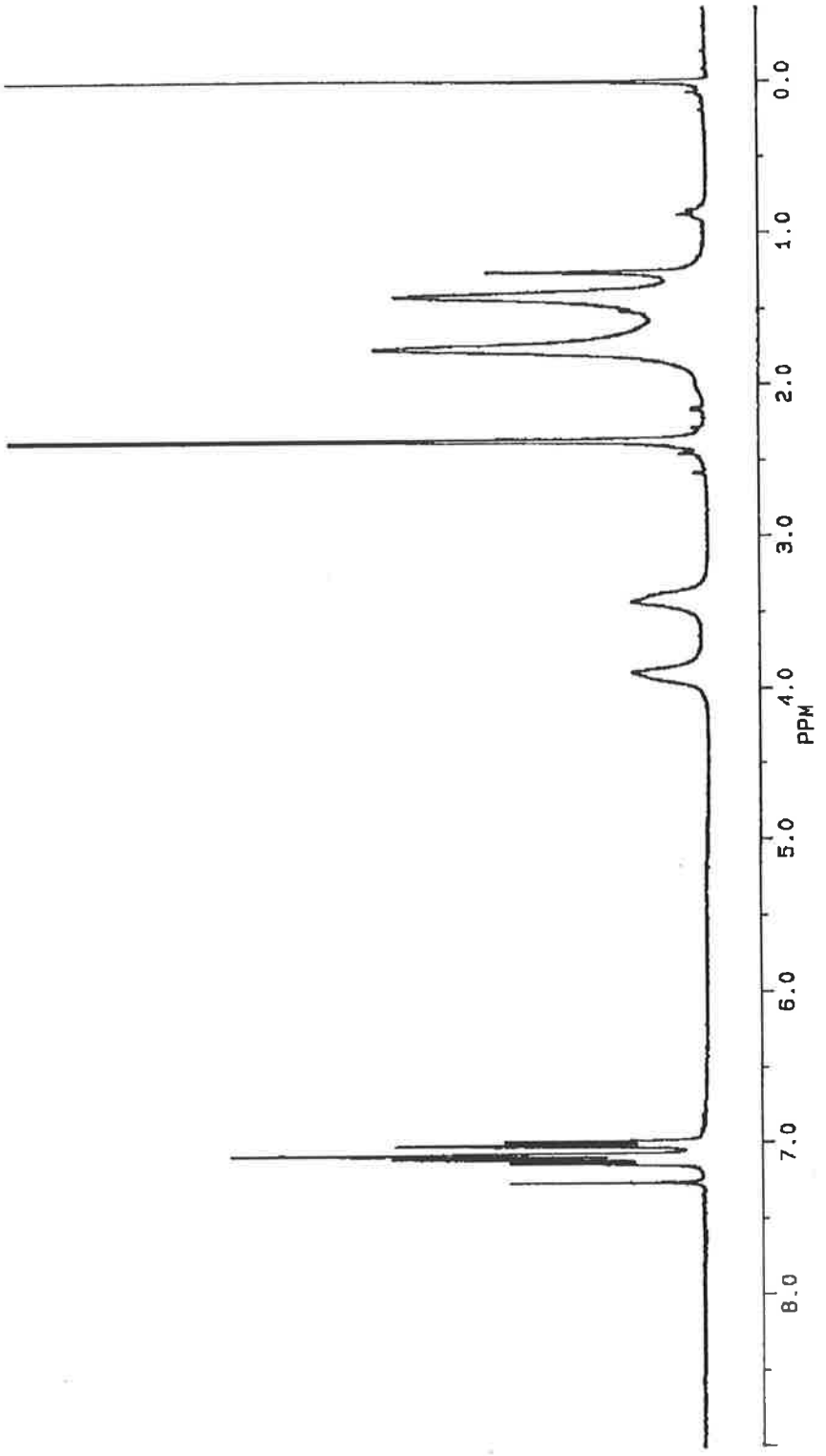
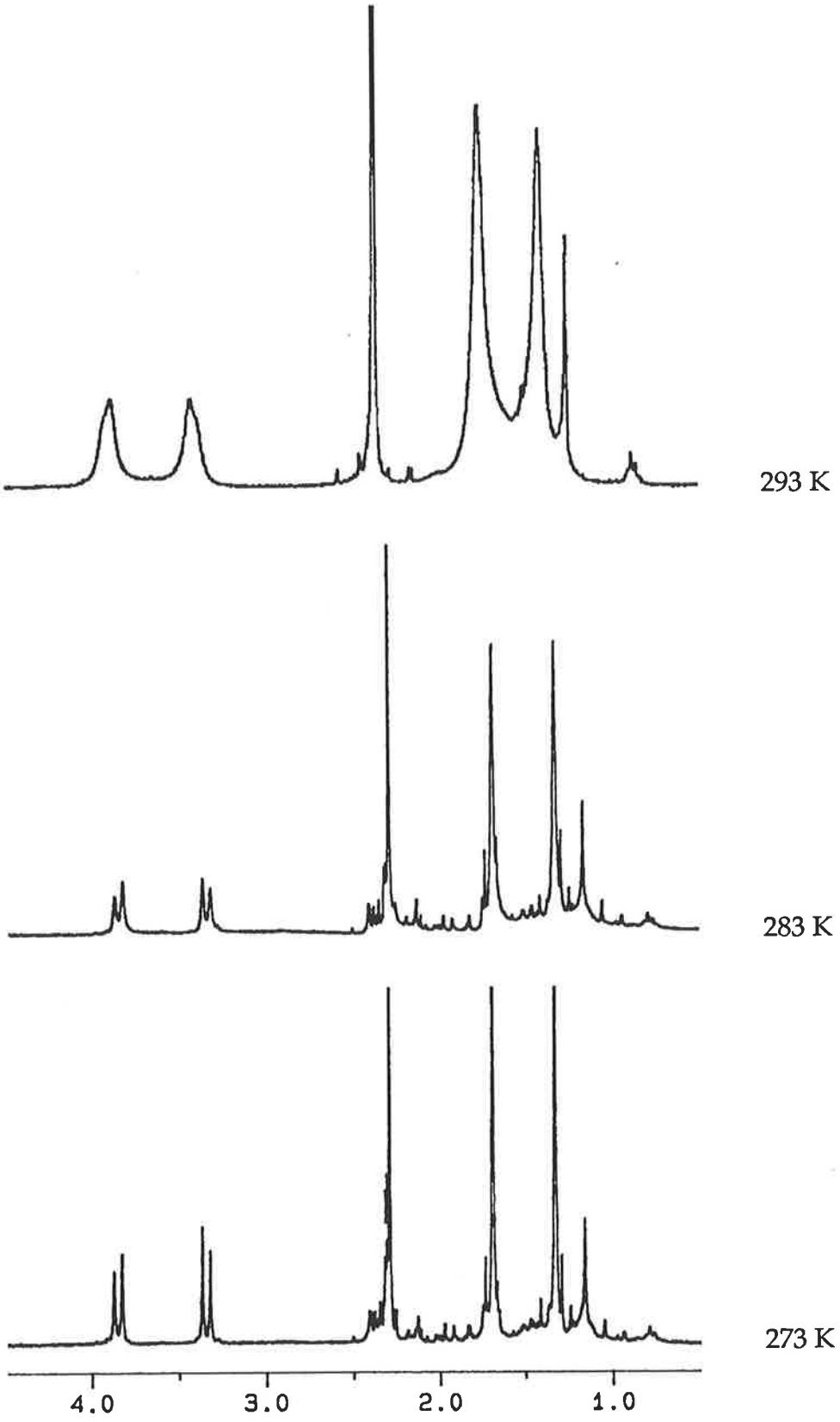
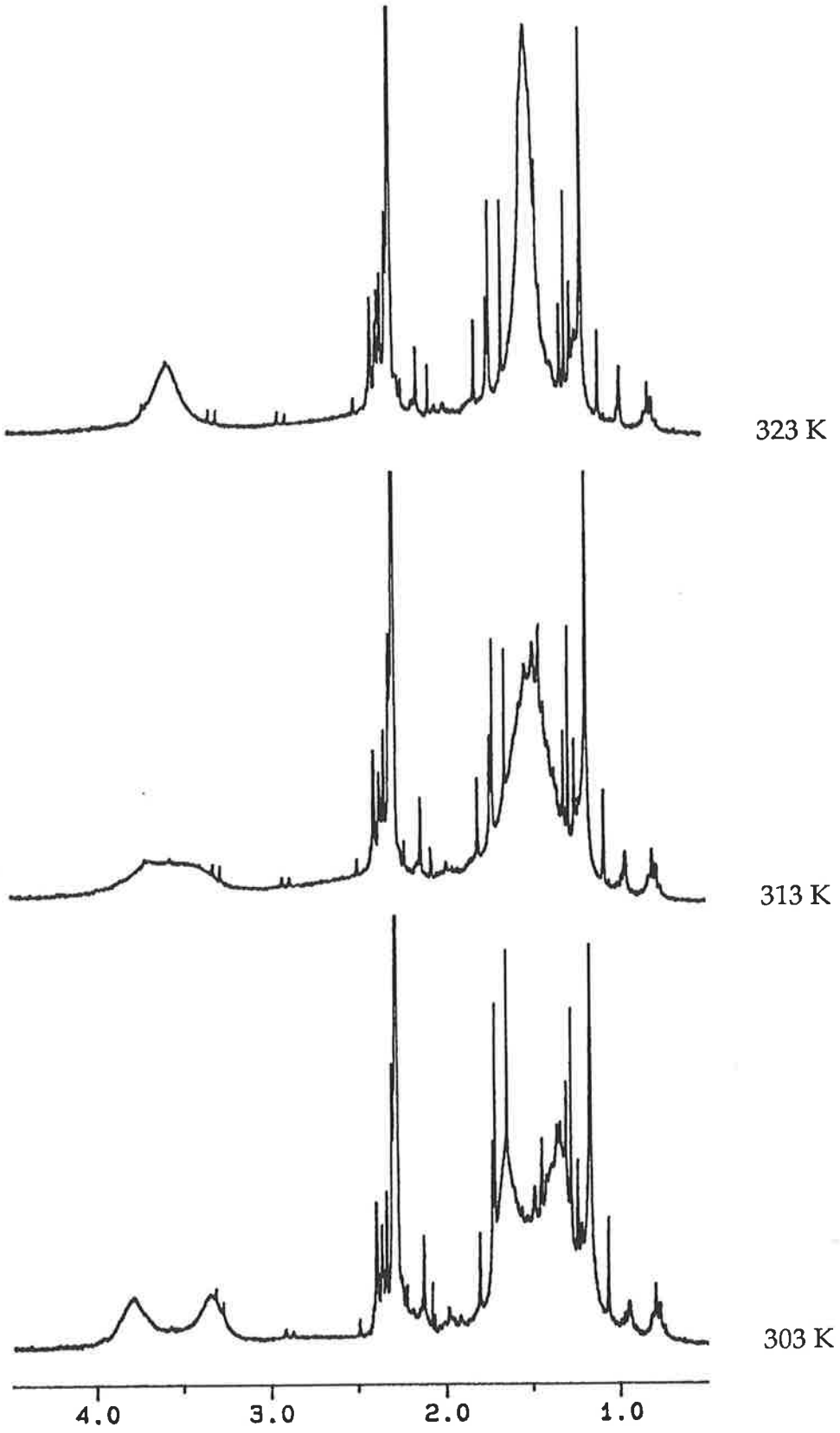
Appendix

Full ^{1}H nmr spectrum for (233) recorded at 293 K



Partial variable temperature ^1H nmr spectra for (233)





Note: small, sharp peaks seen between δ 1.0 and 2.5 ppm are artefacts.