SYNTHETIC APPROACHES TO VIRANTMYCIN AND ANALOGUES

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by

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DEDICATION

This thesis is dedicated to my father, the late Lawrence Claremont Francis. He was a constant source of love, support, encouragement and inspiration.

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ABSTRACT

This thesis describes several synthetic approaches to virantmycin (1). The strategies employed were designed to allow access to analogues of (1). Three different synthetic approaches were investigated.

The first approach involved synthesis of allylic subunits bearing appropriate sidechains, construction of a suitably functionalized aromatic subunit, its coupling with the allylic subunit to provide allylbenzenes and cyclization to form tetrahydroquinolines.

Chapter 1 describes a method for the synthesis of 3,3-disubstituted allylic chlorides of known geometry in which the key reaction is the regio- and stereospecific addition of a Grignard reagent to a suitably substituted alkyne. Using this method, compounds (95), (120) and (123) were prepared cleanly and in good yield.

Chapter 2 details the successful coupling of these allylic chlorides with the aryl cuprate species of (125) to form allylbenzenes (126), (127) and (128). Attempts at electrophile initiated cyclization of (126) and amine (129) to prepare iodotetrahydroquinolines (131) and (130), respectively gave complex mixtures of products.

The second approach, described in Chapter 3, comprised preparation of tertiary, propargylic alcohols with appropriate sidechains, their coupling with an appropriate aromatic subunit, *cis*-hydrogenation of the resulting alkynylbenzenes and cyclization to the required heterocycles. An efficient

synthesis of tertiary, propargylic alcohol (143) is described. The palladium catalysed coupling of 2-methylbut-3-yn-2-ol and (143) with aryl bromides (13) and (14) to provide alkynylbenzenes (146), (147), (148) and (149) is reported. A modified Lindlar reduction of (146) afforded the *cis*-alkene (150) in high yield. Attempts to achieve cyclization of (150) and amine (151) to give dihydroquinolines (153) and (152), respectively, under a variety of conditions, were unsuccessful.

The third approach involved preparation of tertiary, propargylic chlorides bearing appropriate sidechains, their coupling to anilines, functionalization of the triple bonds of the resultant *N*-propargylated compounds and cyclization to give C-3 substituted dihydroquinolines. Chapter 4 describes a preliminary investigation of this approach using model compounds. Copper catalysed coupling of aniline (13) with 3-chloro-3-methylbut-1-yne and chloride (170) provided the *N*-propargylanilines (174) and (175), respectively. Bromination of (174) afforded dibromoalkene (180). Attempts at palladium catalysed cyclization of the vinylstannane derived from (180) *in situ* gave a mixture of products that did not include the desired 3-bromo-1,2-dihydroquinoline (181).

STATEMENT

This thesis contains no material previously submitted for a degree or diploma in any University and to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference is made in the text.

C.L. Francis

NAME: C.L. FRANCIS COURSE: PH.D.

"SYNTHETIC APPROACHES TO VIRANTMYCIN AND ANALOGUES"

I give consent to this copy of my thesis, when deposited in the University Library, being available for loan and photocopying.

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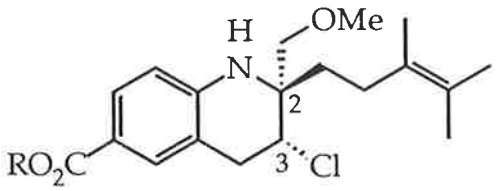
Finally, I am indebted to my family, especially parents Lawrie and Karen and brother Tony, for their continual support, encouragement and understanding throughout the years of my tertiary studies.

INTRODUCTION

Virantmycin (1)[1-9], isolated from the fermentation broth of *Streptomyces nitrosporeus*, is an antibiotic with a novel amino acid structure found to possess potent antiviral activity. It shows inhibitory action against a range of RNA and DNA viruses, apparently by exerting an effect on cell membranes including specific virus receptor sites, suppressing replication of viruses at a very early stage[1]. It also shows weak antifungal activity[1,3] and significant *in vitro* activity against herpes simplex types 1 and 2[1,3].



(1) R=H
(2) R=CH_3

The gross structure of virantmycin was elucidated from its elemental analysis, spectral data[1,2,3] (mainly n.m.r. studies) and by its chemical reactions[2].

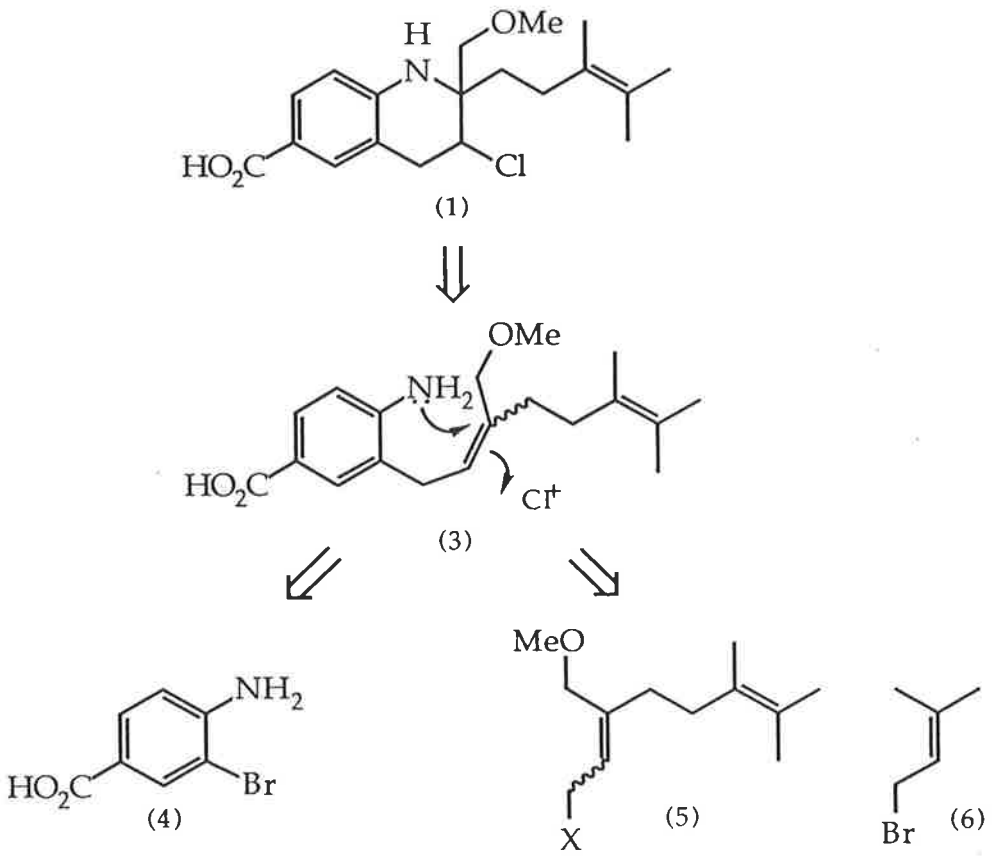
The relative and absolute stereochemistry at the two chiral centres (C-2 and C-3) remained unknown for several years. An X-ray crystallographic determination of the absolute stereochemistry at C-2 and C-3 of (2) was reported to be in progress[2], however, to this time no results have been published.

Virantmycin has been synthesized by two research groups to date[4-8]. Discussion of the details of each synthesis will be deferred until later since all

syntheses were published well after the commencement of work on a considerably different approach by the Adelaide group.

Investigations resulting from these published syntheses revealed the stereochemistry of virantmycin, as determined by n.m.r. spectroscopy utilizing n.O.e. experiments on a synthetic intermediate (ester (2)), to be 2R, 3R[6-9].

Our retrosynthetic analysis of virantmycin suggested that the molecule could be derived from two subunits, (4) and (5) where X is a suitable leaving group, as shown in Scheme 1 below.



Scheme 1

The subunits (4) and (5) could be coupled through metallation of (4) and subsequent reaction with (5) to give the allylbenzene (3). Electrophile initiated cyclization of (3) should produce virantmycin or a derivative thereof.

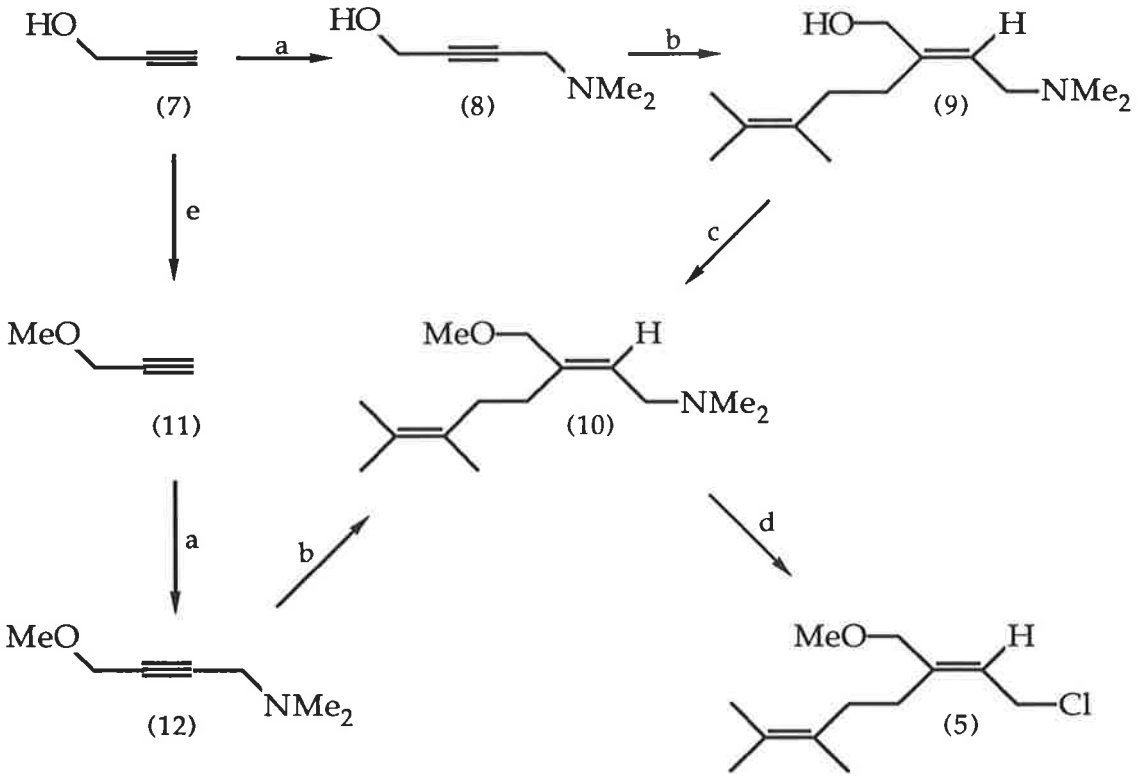
The approach is quite general and should enable a range of analogues of virantmycin to be prepared relatively easily in order to investigate structure-activity relationships. It is planned to have compounds tested by others particularly for antiviral activity. They will also be screened for other biological activity.

Raner[10] has established the conditions for coupling (4) (amine group protected as trifluoroacetamide and carboxyl group masked as a benzyl alcohol function) with 3,3-dimethylallyl bromide (6) as a model for (5) and cyclization of the resulting system[10] but had little success in preparation of the actual virantmycin precursor (5) despite investigations into a number of possible methods.

De Silva investigated a further route to (5) with some success, although his study was incomplete[11]. Because his methods involved several separations of isomers, a more direct route would be desirable. This was the first aim of the present study.

The proposed synthetic route centred on propargyl alcohol (7) as the starting material. This compound could be converted to (5) via a sequence of four steps involving :- (a) a Mannich reaction, (b) a Grignard addition, (c) a methylation and (d) a carbonochloridate cleavage. The order of carrying out

these steps could be varied as shown in Scheme 2 below and part of the current investigation was to determine the most efficient order.



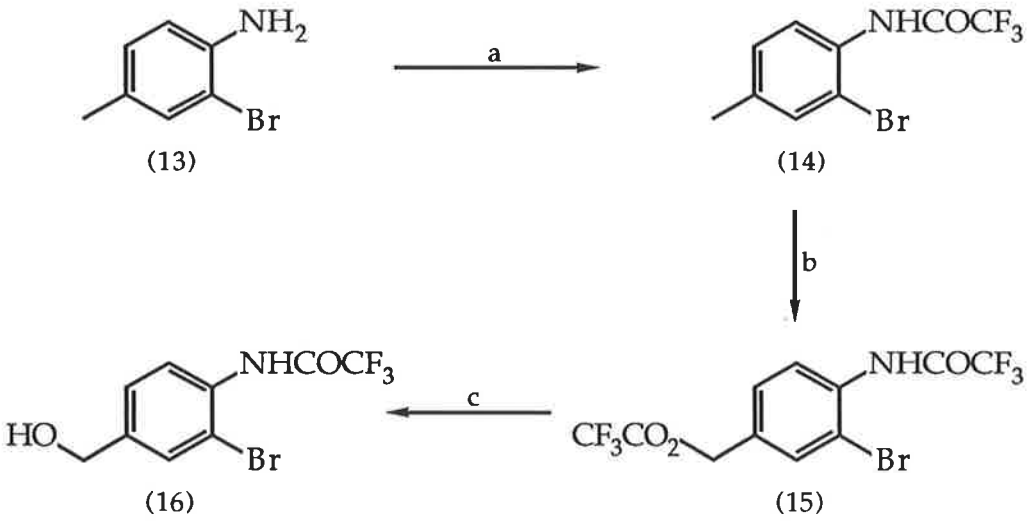
a=$Me_2NH/CH_2O/CuSO_4$, b=$(CH_3)_2C{=}C(CH_3)CH_2CH_2MgBr$, c=$ClCO_2Et/K_2CO_3$
d=NaH/MeI, e=Me_2SO_4/NaOH

Scheme 2

It has been reported that Grignard reagents add to the triple bonds of 4-dialkylaminobut-2-yn-1-ols both regioselectively and stereospecifically (*anti* addition) to produce the *E* alkene in good yield[12,13]. Grignard reagents also add in *anti* fashion to the triple bond of 1-alkoxy-4-aminobut-2-ynes to give the *E* alkene as the major product[13,14].

The Mannich aminomethylations of propargyl alcohol[13,15] and its alkoxy derivatives[13,16] are known to proceed well, as do the carbonochloridate cleavages of allylic, tertiary amines with ethyl chloroformate to give allylic chlorides[13]. It has been shown that the cleavage of the amine C–N bond in these reactions does not affect the stereochemistry of the double bond[13]. Hence Scheme 2 should provide a way of synthesizing compound (5) with known geometry.

Raner[10] has established the conditions for a high yield synthesis of a suitable aromatic subunit (Scheme 3).

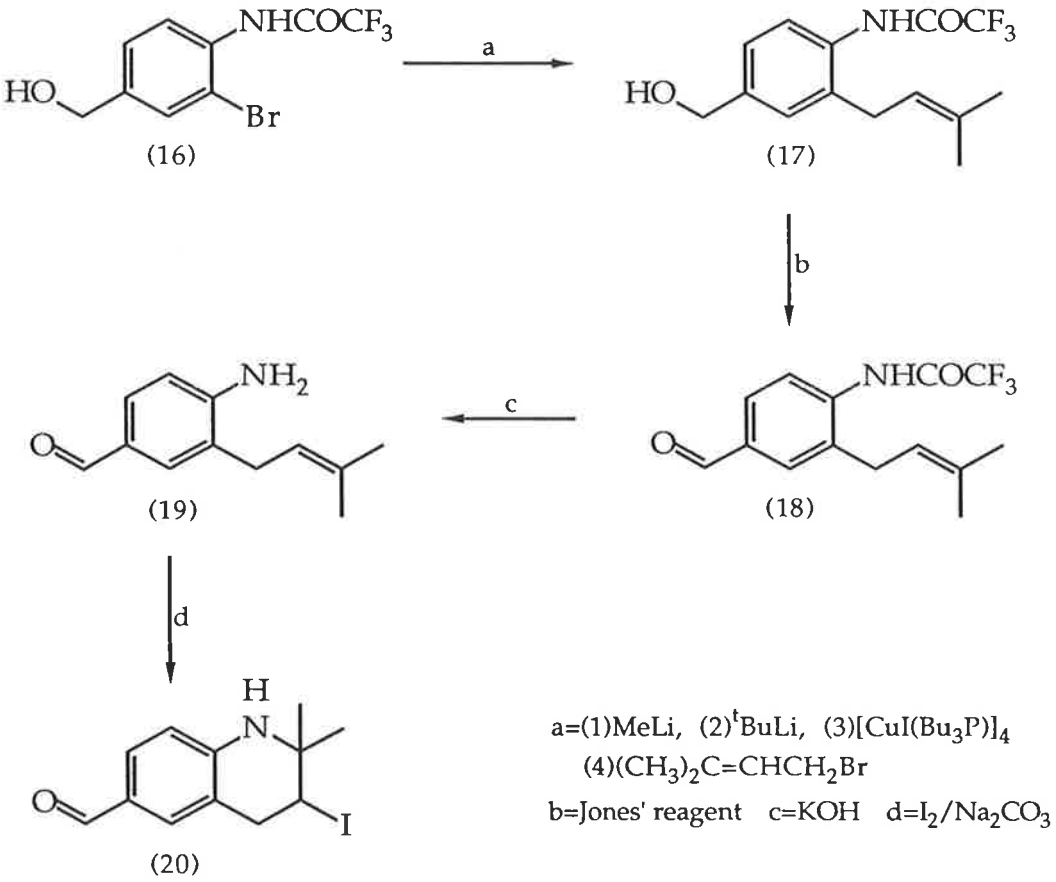


a=$(CF_3CO)_2O$, b=$K_2S_2O_3/CuCO_3/CF_3CO_2H$, c=$KHCO_3$

Scheme 3

Trifluoroacetylation of commercially available 2-bromotoluidine (13) gave amide (14) which was oxidized at the benzylic position to provide the trifluoroacetate (15). After hydrolysis of the ester function, the trifunctional, possible virantmycin precursor (16) was obtained.

Raner[10] also carried out model coupling and cyclization reactions using subunit (16) and 3,3-dimethylallylbromide (6) (as a model for (5)) to produce tetrahydroquinolines, such as (20), which have the basic virantmycin skeleton (Scheme 4).



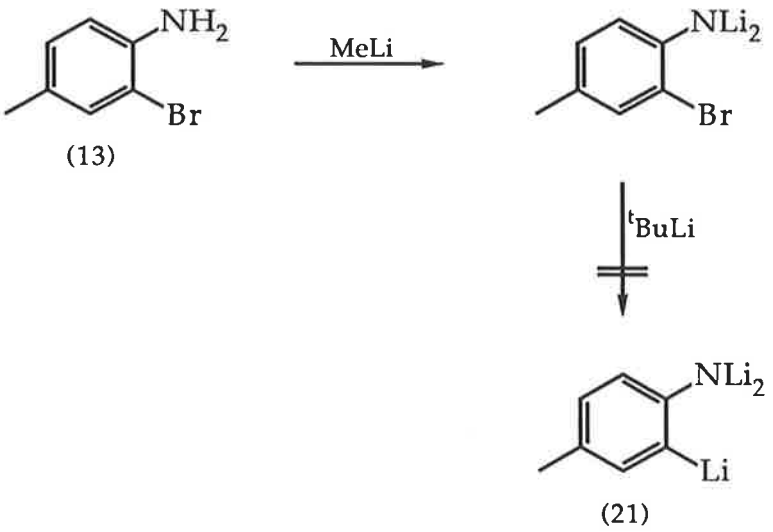
Scheme 4

The amidoalcohol (16) was coupled with 3,3-dimethylallylbromide (6) via the aryl cuprate species to form the allylbenzene (17). After oxidation of this compound to the corresponding aldehyde (18), hydrolysis of the

trifluoroacetamide group liberated the free amine (19). Iodine-initiated cyclization of (19) provided the iodotetrahydroquinoline (20).

The synthetic route outlined in Schemes 3 and 4 above was chosen after Raner's investigation of several variations[10], which are described below.

It was found necessary to protect the amino function as an amide during the course of the metallation, since on attempted formation of the aryllithium species (21) from bromoamine (13) by treatment with two equivalents of methyllithium followed by two equivalents of *tert.*-butyllithium in tetrahydrofuran at −78°, only the starting bromoamine (13) was recovered (Scheme 5).



(13)

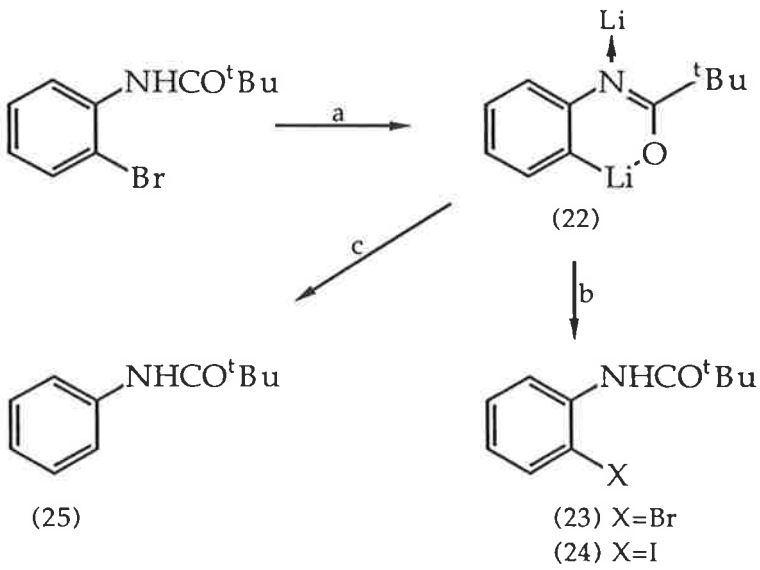
(21)

Scheme 5

It was presumed that the trilithio species (21) was reluctant to form due to adverse electrostatic interactions in what is formally a trianion[10]. The amide

protecting group should have no acidic α–protons so that the problem of undesirable aldol-type condensations is avoided and the trifluoroacetamide was preferred to the pivalamide (which was also used in some of the studies) due to its comparative ease of removal[10].

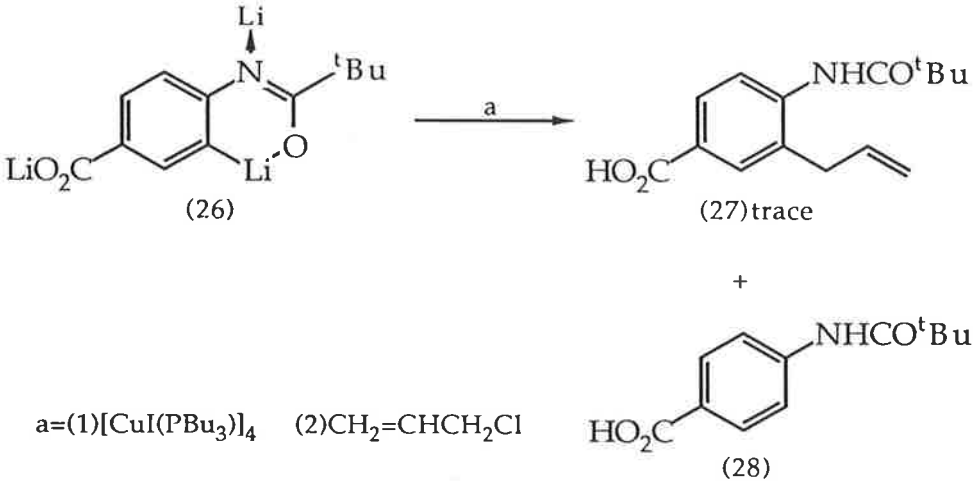
Use of the corresponding aryl cuprate was required since the aryllithium species (22) was found to undergo a lithium-halogen exchange (in preference to substitution) when reacted with allyl bromide or allyl iodide in tetrahydrofuran at –78° and the corresponding halobenzenes (23) or (24) were recovered[10]. If allyl chloride was used at –78° or higher temperatures no reaction occurred and only the reduced compound (25) was recovered (Scheme 6)[10].



a=(1)MeLi, (2)=^{t}BuLi b= CH_2=$CHCH_2$X (X=Br,I) c= CH_2=$CHCH_2$Cl

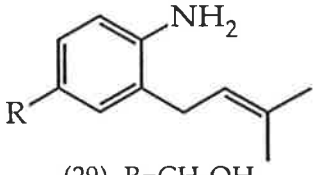
Scheme 6

Masking of the carboxyl function as the hydroxymethyl group was needed in order for efficient coupling to occur, since when the arylcuprate species derived from (26) was reacted with allyl chloride in tetrahydrofuran at –78° or higher temperatures, only a trace of desired product (27) was observed after workup. The predominant product was the reduced compound (28) (Scheme 7)[10].



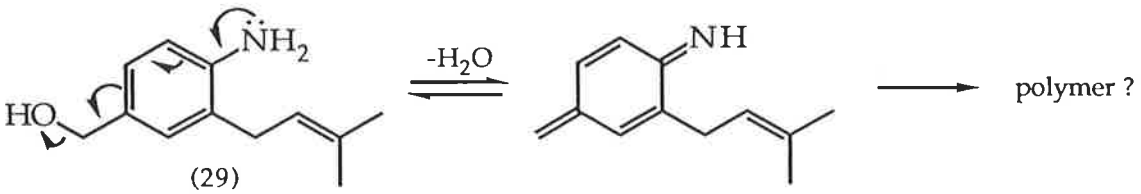
Scheme 7

The aldehyde (19) was the substrate of choice for the iodine-initiated cyclization reaction since the procedure was found to be incompatible with the hydroxymethyl substituted aniline (29)[10].



(29) R=CH_2OH
(30) R=H

When (29) was stirred with iodine and sodium carbonate in dichloromethane it underwent decomposition possibly due to formation of hydrogen iodide as a by-product of the reaction. This presumably could convert the benzylic alcohol to an iodide which would then react with the amine thus undergoing undesirable condensation reactions[10]. Alternatively, elimination of water could occur, resulting in a quinone-type system which probably would polymerize.

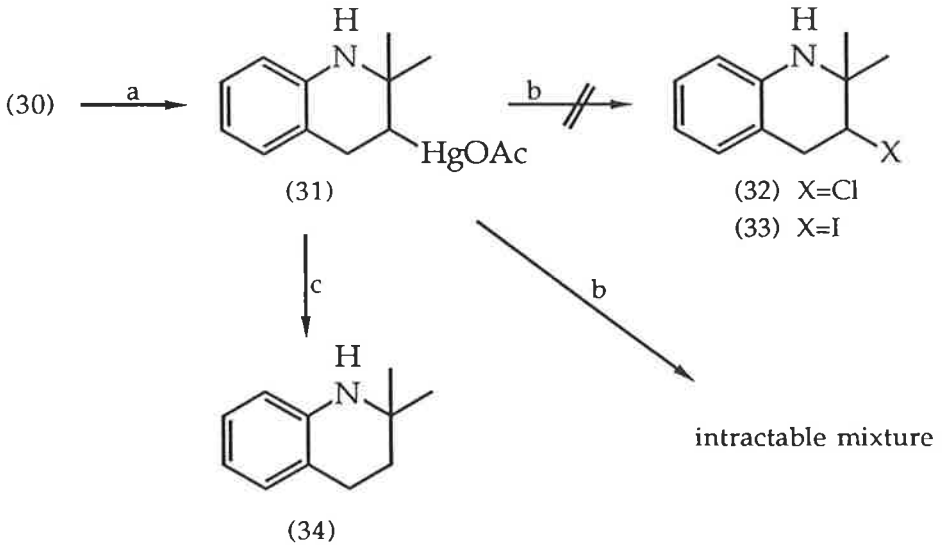


(29)

In repetitions of the reaction, using either triethylamine as a buffer or aqueous sodium carbonate in a two-phase system, decomposition was still observed[10].

Raner[10] investigated a variety of electrophiles and concluded that iodine was the most appropriate. Treatment of (30) with either chlorine or bromine as electrophile even at a low reagent concentration led to a complex mixture of aromatic ring halogenated products as well as dihalides arising from simple addition of the halogen to the alkene side chain[10]. Reaction of (30) with three equivalents of mercuric acetate in aqueous acetone afforded the unstable organomercurial derivative (31); however this could not be chlorinated to form the desired chlorotetrahydroquinoline (32)[10]. Introduction of one equivalent of chlorine in carbon tetrachloride to the crude reaction mixture

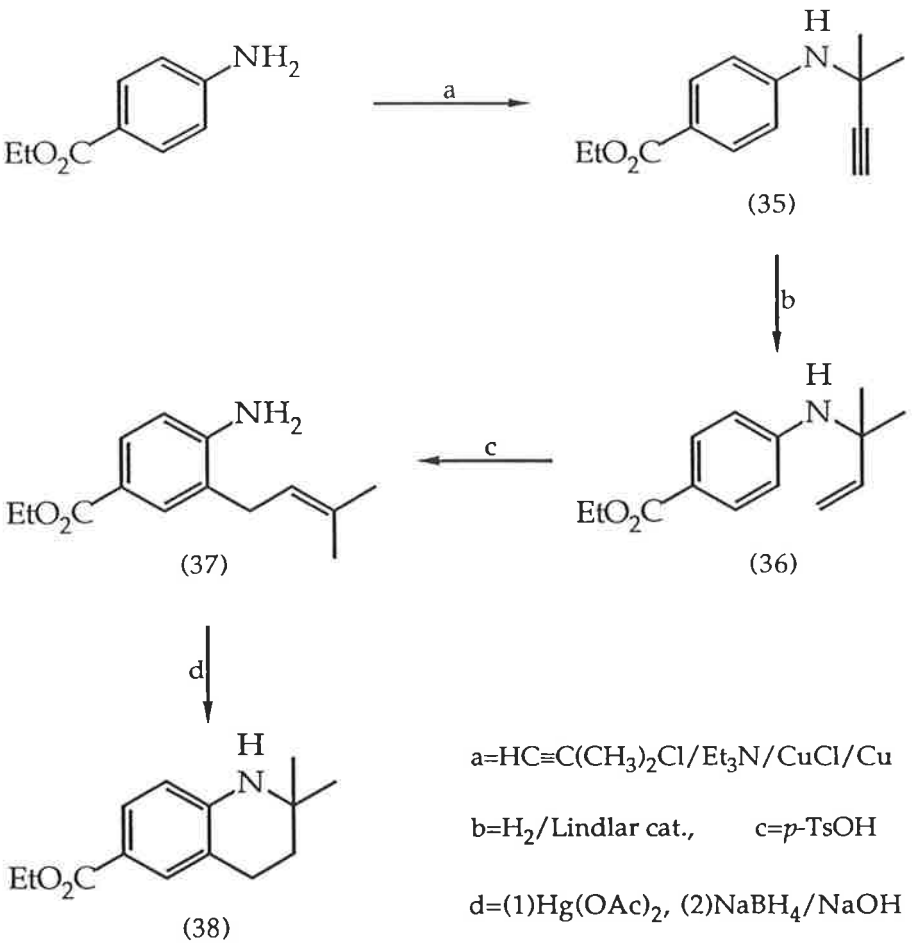
((31) was too unstable to be isolated) resulted in an intractable mixture[10]. Attempted bromination and iodination were found to be no more productive[10]. The only way Raner[10] found to produce a stable tetrahydroquinoline from (31) was by the use of a reductive workup with alkaline sodium borohydride. This produced compound (34) in high yield (Scheme 8).



a=$Hg(OAc)_2$, b=$X_2/h\nu$ (X=Cl,Br,I), c=$NaBH_4/NaOH$

Scheme 8

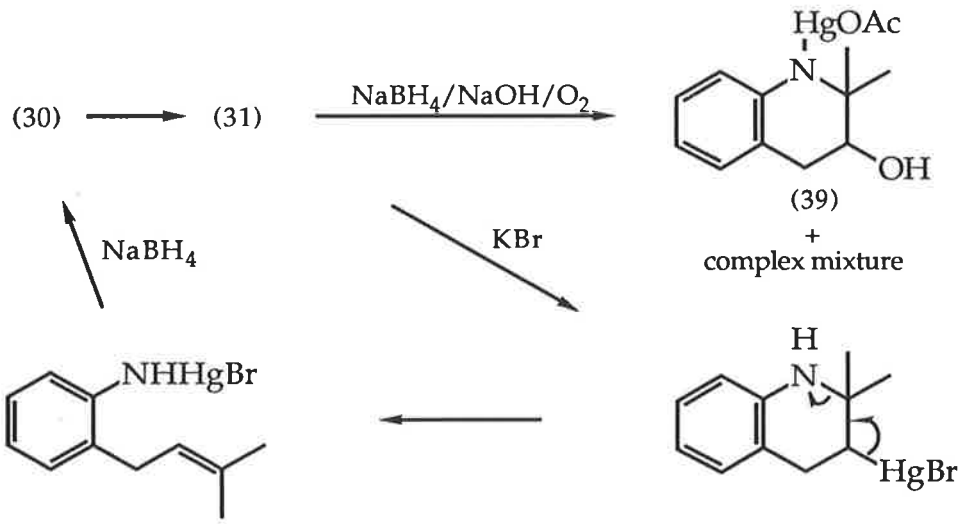
Cooper[17] applied this method to the cyclization of allylanilino ester (37), prepared via the sequence of reactions shown in Scheme 9, to produce tetrahydroquinoline (38).



Scheme 9

Reaction of ethyl *para*-aminobenzoate with 3-chloro-3-methylbut-1-yne in the presence of triethylamine, cuprous chloride and copper/bronze powder produced the *N*-substituted aminobenzoate (35). Hydrogenation using Lindlar catalyst afforded the corresponding *N*-allyl derivative (36). Amino-Claisen rearrangement of this compound using a catalytic amount of *para*-toluenesulphonic acid in aqueous acetonitrile provided (37). Treatment of (37) with three equivalents of mercuric acetate, followed by reductive workup with alkaline, sodium borohydride resulted in formation of the tetrahydroquinoline (38).

Cooper[17] investigated oxygenation of the organomercurial acetate (31). Formation of (31) from (30) using Raner's[10] procedure, followed by treatment with alkaline sodium borohydride in the presence of excess oxygen gas gave a complex product mixture[17]. The spectral data indicated the presence of (39) in the mixture although the yield was very poor (Scheme 10)[17]. Attempted conversion of (31) to the corresponding bromide derivative using potassium bromide returned the starting allylaniline (30)[17]. It is possible that the organomercurial bromide has increased radical affinity which facilitates decomposition back to (30) (Scheme 10)[17].

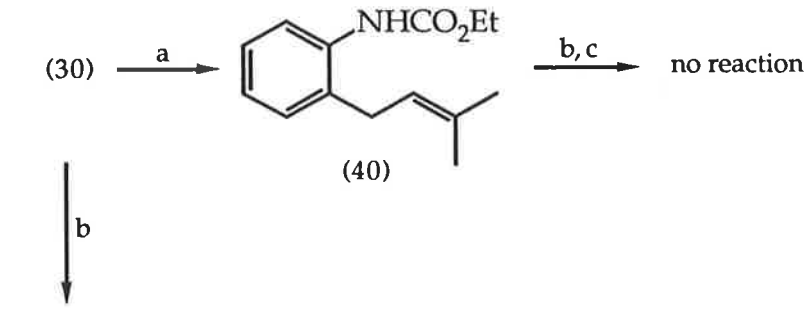


Scheme 10

Attempts to convert (31) to a halogenated species via radical reaction with *N*-bromosuccinimide or sulphuryl chloride were unsuccessful[17].

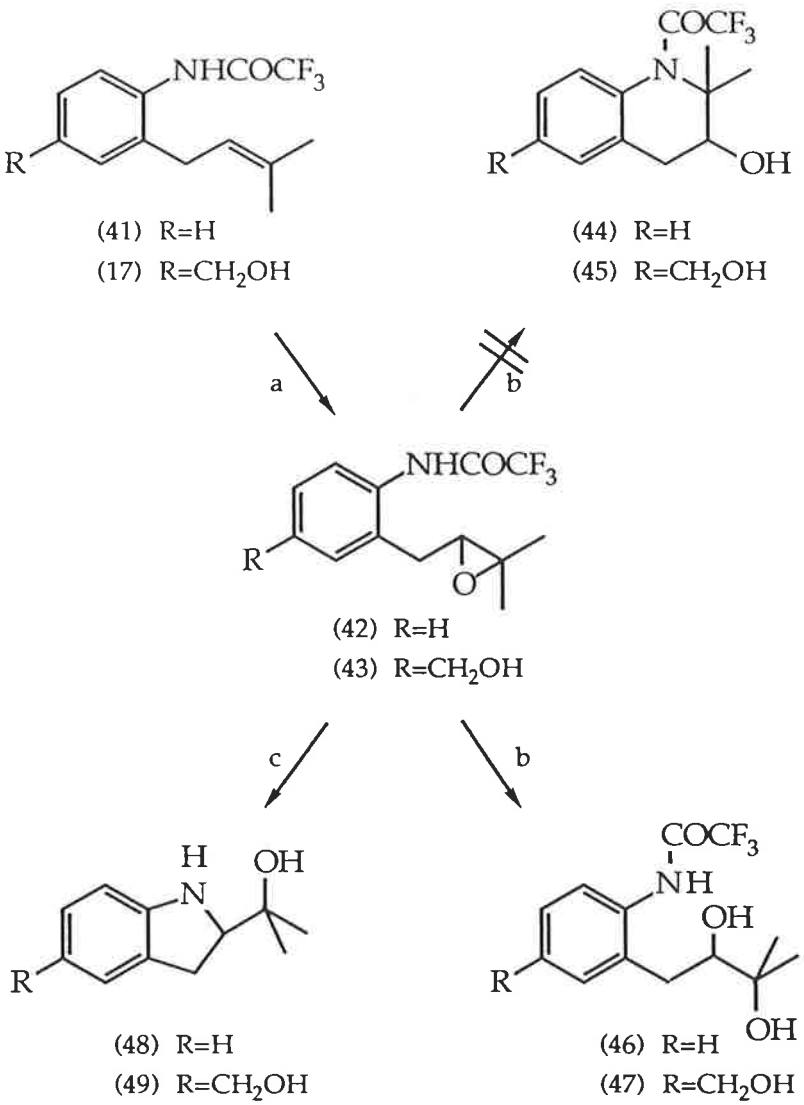
Cooper[17] also evaluated the use of mercuric nitrate as electrophile in the cyclization reaction. Both (30) and carbamate (40) proved to be unreactive

toward mercuric nitrate (Scheme 11)[17]. The carbamate (40) also failed to react with mercuric acetate[17].



Scheme 11

Raner[10] also considered boron trifluoride etherate as electrophile in ring closure reactions of epoxides such as (44). The epoxide (42), formed by stirring (41) with *meta*-chloroperbenzoic acid in dichloromethane, did not give the desired product (44) when treated with boron trifluoride etherate in ether[10]. Instead, the glycol (46) was produced, presumably not during the attempted cyclization reaction, but during the aqueous workup procedure[10]. The glycol (47) was produced analogously from (17) (Scheme 12)[10]. Base-catalysed epoxide cyclization reactions were no more productive, since treatment of (42) with methanolic potassium carbonate afforded the dihydroindole (48) instead of the desired tetrahydroquinoline (44)[10]. Similarly, (49) was produced from (43) (Scheme 12)[10].



(41) R=H
(17) R=CH_2OH

(44) R=H
(45) R=CH_2OH

(42) R=H
(43) R=CH_2OH

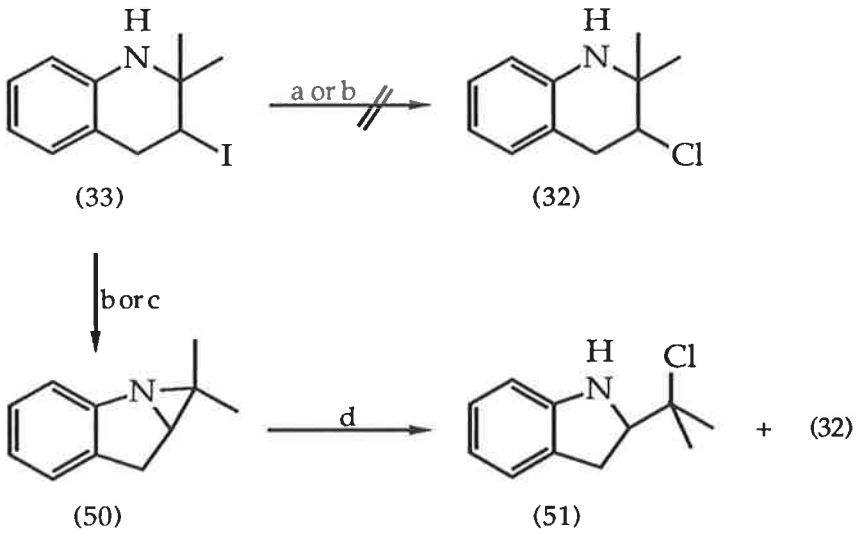
(48) R=H
(49) R=CH_2OH

(46) R=H
(47) R=CH_2OH

a=MCPBA, b=(1)$BF_3.OEt_2$, (2)H_2O, c=K_2CO_3

Scheme 12

During his study of the iodine-initiated cyclization reactions, Raner[10] considered the possible preparation of the chloride (32) by substitution of the iodide (33) (Scheme 13).



a=LiCl, b=AgCl, c=NaH, d=HCl(g)

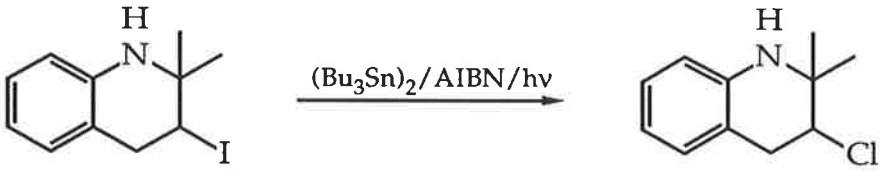
Scheme 13

Heating (33) to 50° with lithium chloride in dimethyl sulphoxide caused no substitution even over prolonged periods of time[10]. Stirring (33) with silver chloride in acetone, with the aim of abstracting the iodide ion, provided not the expected chloride (32) but the aziridine (50) arising from intramolecular substitution (Scheme 13)[10]. A more rapid and cleaner procedure to form (50) involved treatment of the chloride (33) with one equivalent of sodium hydride in tetrahydrofuran at 0°[10].

Having obtained the aziridine, Raner[10] investigated its possible conversion to the chloride (32). Treatment of (50) with gaseous hydrogen chloride in dichloromethane at room temperature met with mixed success. An inseparable mixture of the chlorides, tetrahydroquinoline (32) and dihydroindole (51), was obtained (Scheme 13)[10].

It has been reported that similar aziridine ring openings with excess of trifluoroacetic acid gave the six-membered ring product exclusively[18] and indeed this method was later used in a total synthesis of virantmycin[7,8].

Since Raner was unable to replace the iodo moiety of tetrahydroquinoline (33) with chlorine via nucleophilic displacement, Cooper investigated whether or not the transformation was possible using a radical process[19]. Reaction of (33) with excess of hexabutyldistannane and a trace of azobisisobutyronitrile in carbon tetrachloride under irradiation for 48 h resulted in formation of chloroamine (32) in moderate yield (Scheme 14)[19].



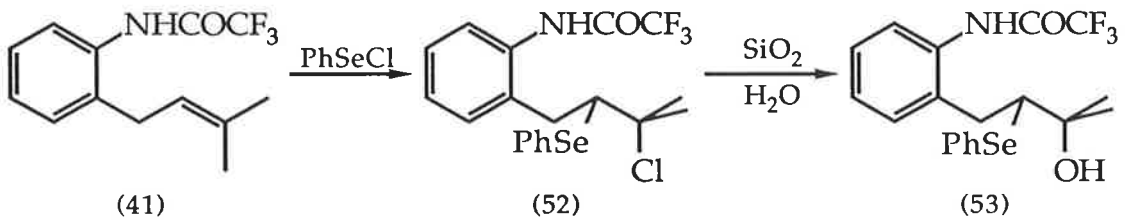
(33) (32)

Scheme 14

It is therefore apparent that a radical displacement reaction may hold promise as a facile procedure for the introduction of chlorine into tetrahydroquinoline systems such as (33). The extension of this methodology to the synthesis of virantmycin and analogues may be possible.

Selenium-induced cyclization of *N*-protected derivatives of allylaniline (30) was studied by Cooper[19]. The trifluoroacetamide (41) was treated with phenylselenenyl chloride, dry silica gel and anhydrous potassium carbonate in dichloromethane. No cyclized material was evident after 4 days reaction

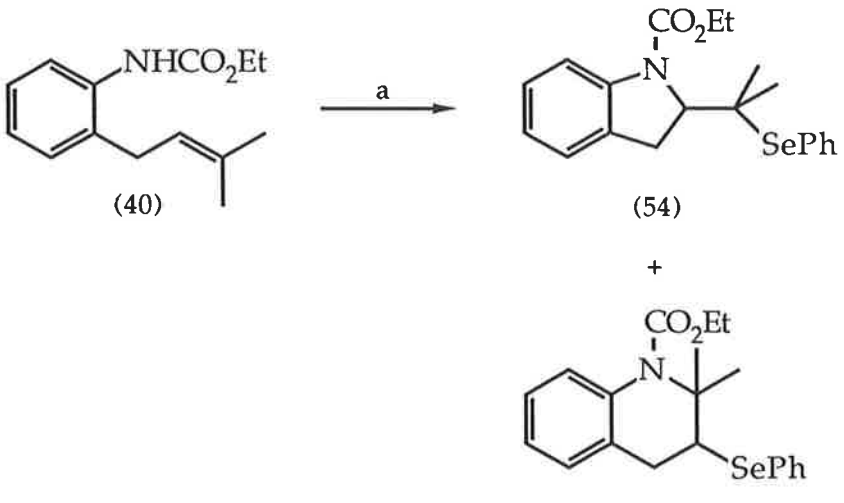
time but it was possible to isolate the hydroxyselenide (53) in low yield by chromatography[19]. This compound was thought to arise from displacement of the chloride (52) on silica (Scheme 15)[19].



(41) (52) (53)

Scheme 15

Reaction of carbamate (40) with one equivalent of phenylselenenyl chloride, dry silica gel and anhydrous potassium carbonate in dichloromethane for 3 days produced a 1:1 mixture of dihydroindole (54) and tetrahydroquinoline (55) which could not be separated by chromatography (Scheme 16)[19].

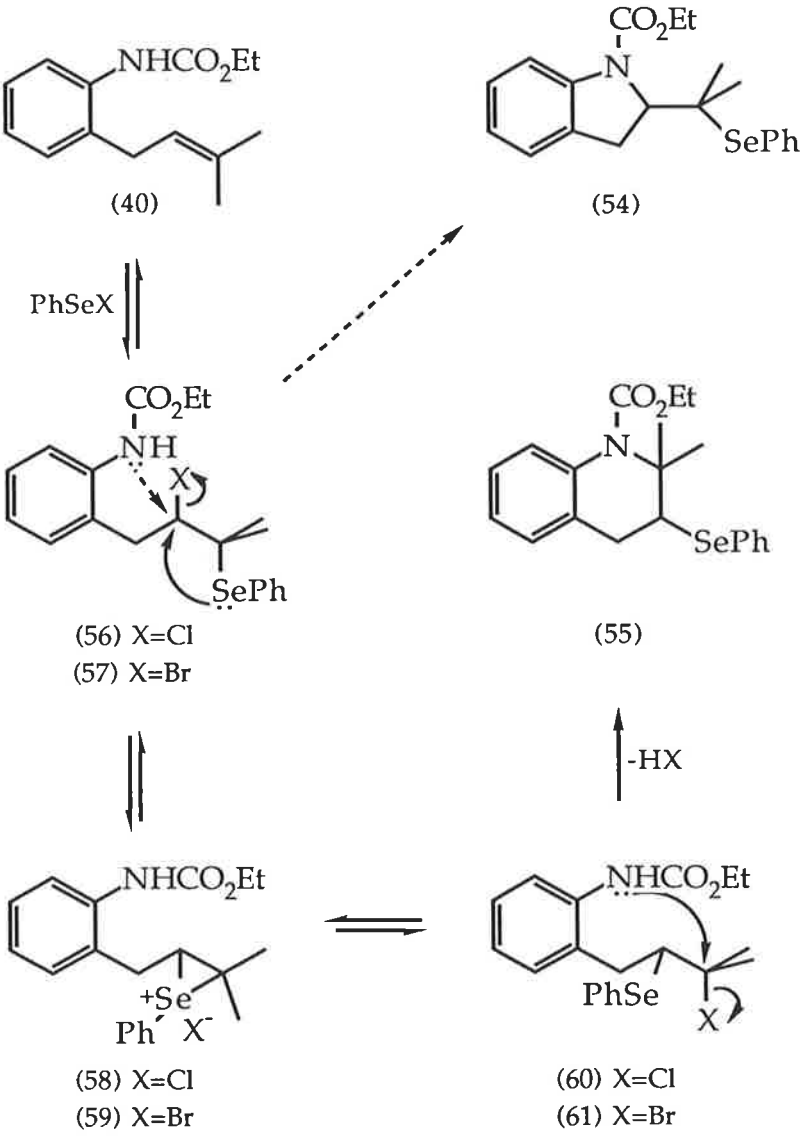


(40) (54) + (55)

a=PhSeCl/K_2CO_3/silica

Scheme 16

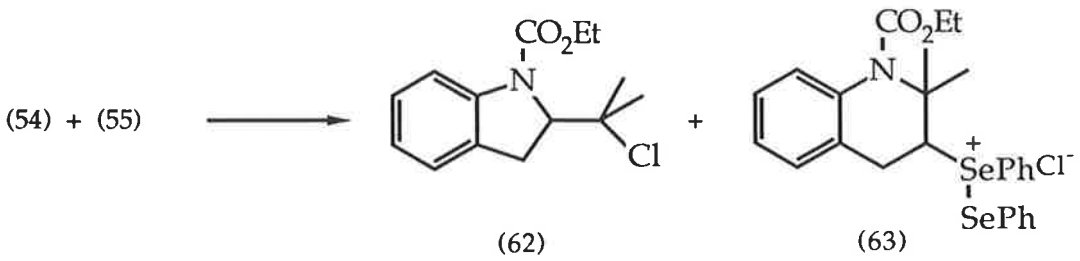
The compounds (54) and (55) correspond to the kinetic and thermodynamic products respectively[19]. The dihydroindole (54) arises from cyclization of the initial *anti*-Markovnikov phenylselenenyl adduct (56) and the tetrahydroquinoline (55) from cyclization following rearrangement of the *anti*-Markovnikov adduct to the thermodynamically more stable adduct (60) via an episeleniranium intermediate (58) (Scheme 17)[19].



Scheme 17

Reaction of (40) with phenylselenenyl bromide, which is a less reactive species than the chloride[19], for 6 days gave only the dihydroindole (54). The selectivity was attributed to the relative abundance of the precursors to cyclization. The larger size of the bromide anion (relative to chloride) precludes it from attack at the hindered tertiary centre of the intermediate (59). This results in a predominance of the adduct (57) which, in turn, leads to selective formation of the dihydroindole (54) (Scheme 17)[19].

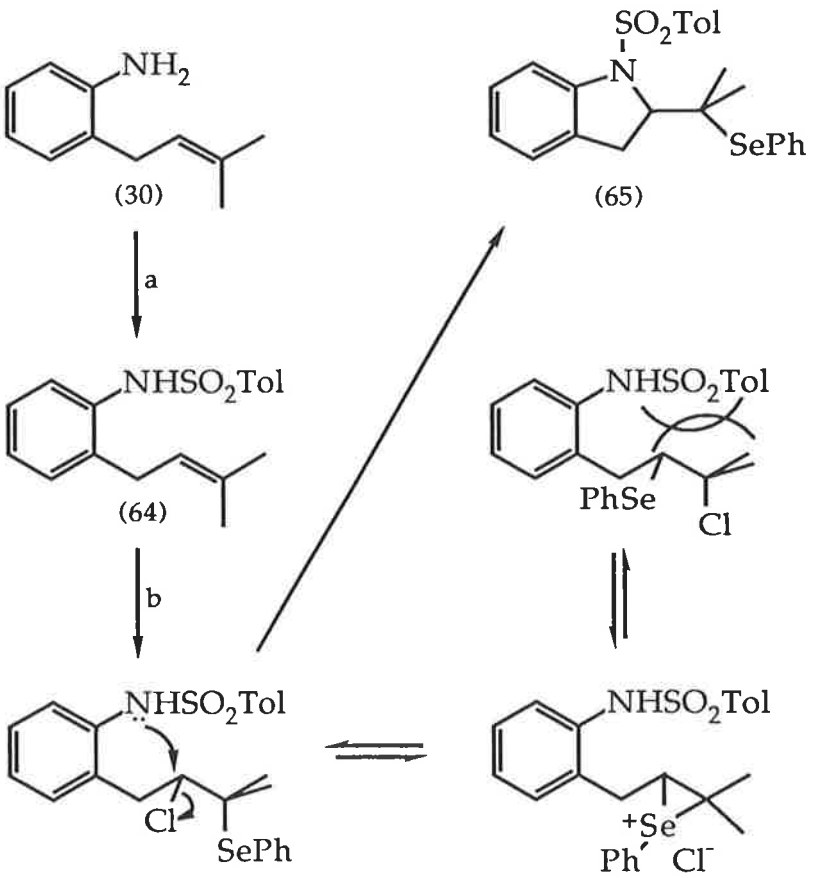
Cooper[19] envisaged that the selenides (54) and (55) could be converted to their chloro-substituted derivatives using established methodology. However, reaction of the selenide mixture with tetrabutylammonium chloride and chorine at −22° gave a complex mixture of products, from which it was possible to isolate the chlorodihydroindole (62) by chromatography (Scheme 18)[19]. Reaction of selenides (54) and (55) with phenylselenenyl chloride at −78° also gave a mixture of products, from which it was possible to isolate, by h.p.l.c., (62) and the selenonium salt (63) as a crystalline solid which rapidly decomposed (Scheme 18)[19]. When the reaction was followed by h.p.l.c. it was seen that the salt (63) decomposed in preference to reaction with chloride ion, to give many unidentifiable products[19].



(62) (63)

Scheme 18

The effect of the *para*-toluenesulphonamide protecting group on the selenium induced cyclization reaction was also studied[19]. Treatment of the sulphonamide (64) with phenylselenenyl chloride at room temperature for 64 h gave only the dihydroindole (65), the structure of which was confirmed by X-ray crystallography[19]. This selectivity was again attributed to a steric effect, with the bulky tosyl group being too sterically hindered to undergo *endo* cyclization, which necessitates attack on a tertiary centre (Scheme 19)[19].



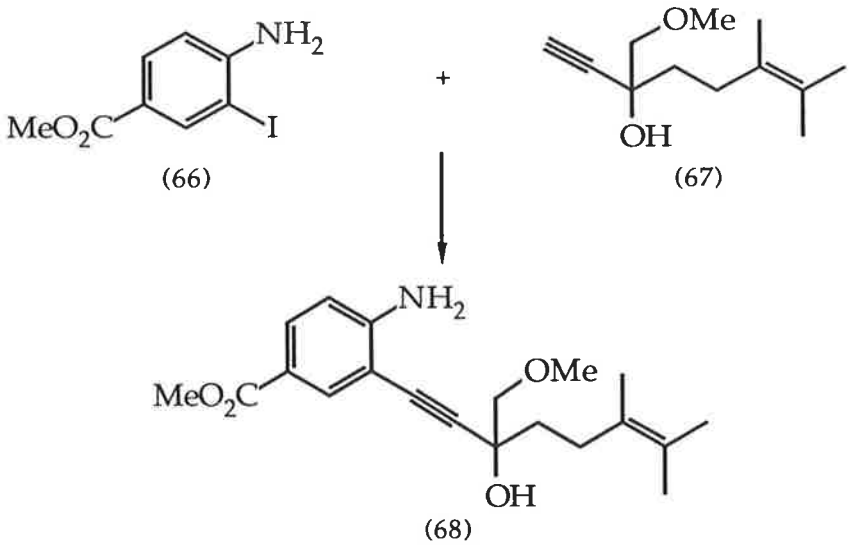
a=TsCl/py, b=PhSeCl

Scheme 19

The results from Coopers' selenium-induced cyclization studies[19] detailed above suggest that whilst this process may be a useful way to prepare dihydroindole systems, it could not be the method of choice for the synthesis of virantmycin and analogues since these require formation of a tetrahydroquinoline skeleton.

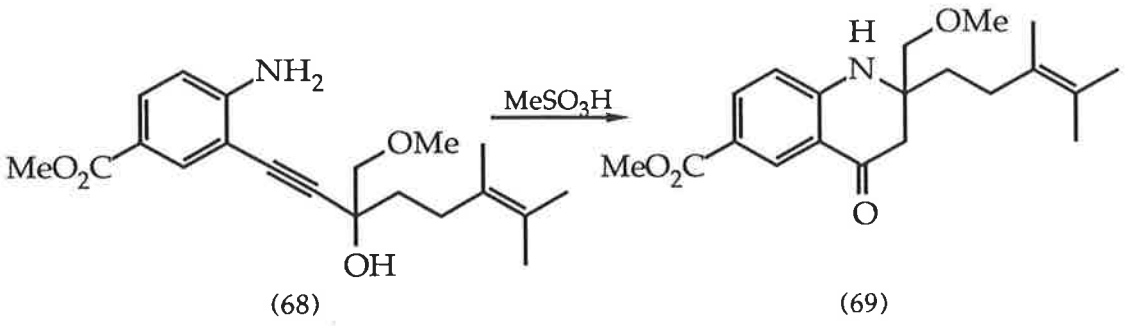
The second aim of the present study was to synthesize the aromatic subunit, using Raner's[10] methods, couple it to the allylic subunit (as well as compounds closely structurally related) and study cyclizations of these compounds using knowledge gained from Raner's[10] and Cooper's[17,19] investigative work. This was expected to lead to synthesis of virantmycin and a range of analogues.

As stated earlier, two research groups have reported syntheses of virantmycin to date[4-8]. In 1986, a synthesis of (±)-virantmycin by Hill and Raphael[4,5] was published in which the first key step was coupling of the iodoester (66) with the acetylenic alcohol (67) to produce (68), carried out by reaction in diethylamine with a catalytic quantity of *bis*(triphenylphosphine)palladium(II) chloride in the presence of cuprous iodide (Scheme 20). This coupling differs from that in our intended synthesis in which an aryl cuprate is coupled with an allylic halide.



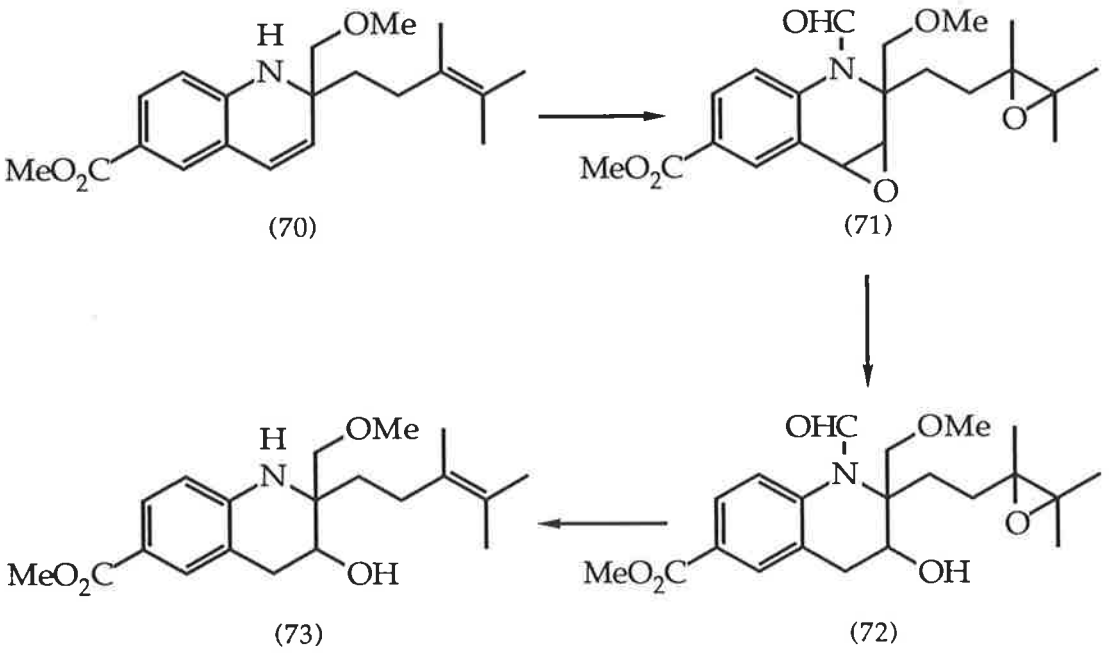
Scheme 20

The second key step in the synthesis was cyclization of the aminoester (68) with methanesulphonic acid to form (69) (Scheme 21). Subsequent manipulation of functionality in the heterocyclic ring produced virantmycin methyl ester. Again, this method differs from our intended synthesis in which functionality is introduced directly to C-3 at the time of cyclization in the one step. Our approach should enable a shorter elaboration to virantmycin.



Scheme 21

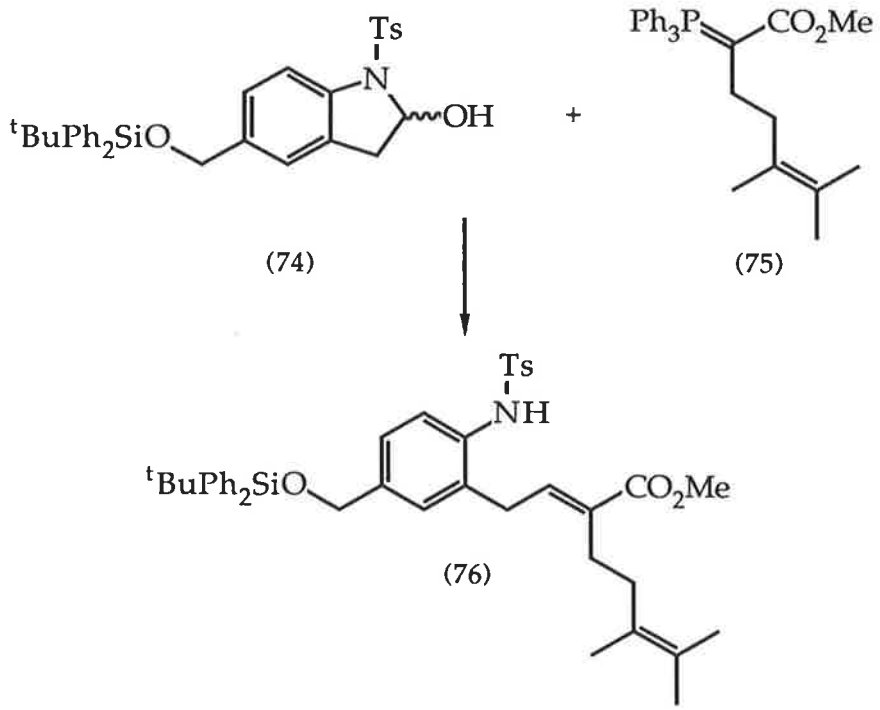
In the Cambridge sequence, borohydride reduction of (69) followed by dehydration using triphenylphosphine/carbon tetrachloride yielded (70) which proved to be thermally unstable readily losing the elements of dimethyl ether to give the corresponding quinoline. Accordingly the synthesis was continued with the more stable *N*-formyl derivative of (70). The formamide was treated with excess of *meta* -chloroperbenzoic acid to give a diastereomeric mixture of epoxides (71), which without separation, was hydrogenolysed to yield hydroxyepoxide (72). De-epoxidation of (72) using tungsten hexachloride/butyllithium followed by deformylation gave a single diastereomer of aminoalcohol (73) (Scheme 22). Chlorination of (73) followed by ester hydrolysis provided a chloroacid identical in all chromatographic and spectroscopic respects to natural virantmycin.



Scheme 22

Oxidation of the *N*-formyl derivative of (73) followed by borohydride reduction and deformylation yielded predominantly the other diastereomer of (73). Chlorination of this compound gave a product whose ^{1}H n.m.r. spectrum was significantly different to that of authentic virantmycin methyl ester. No unambiguous indication of the relative stereochemistry at C-2 and C-3 of virantmycin is given by the spectroscopic properties of these compounds.

A total synthesis of antipodal virantmycin by Shirahama *et al* [6] was published in 1988. The first key step involved coupling of two subunits, hemiacetal (74) and phosphorane (75) (both prepared by multi-step syntheses), in a Wittig reaction, to produce (*E*)-αβ–unsaturated ester (76) and its *Z*-isomer in a *ca*. 30:1 ratio (Scheme 23). This coupling step also differs from that in our intended synthesis where an aryl cuprate species is coupled with an allylic halide.

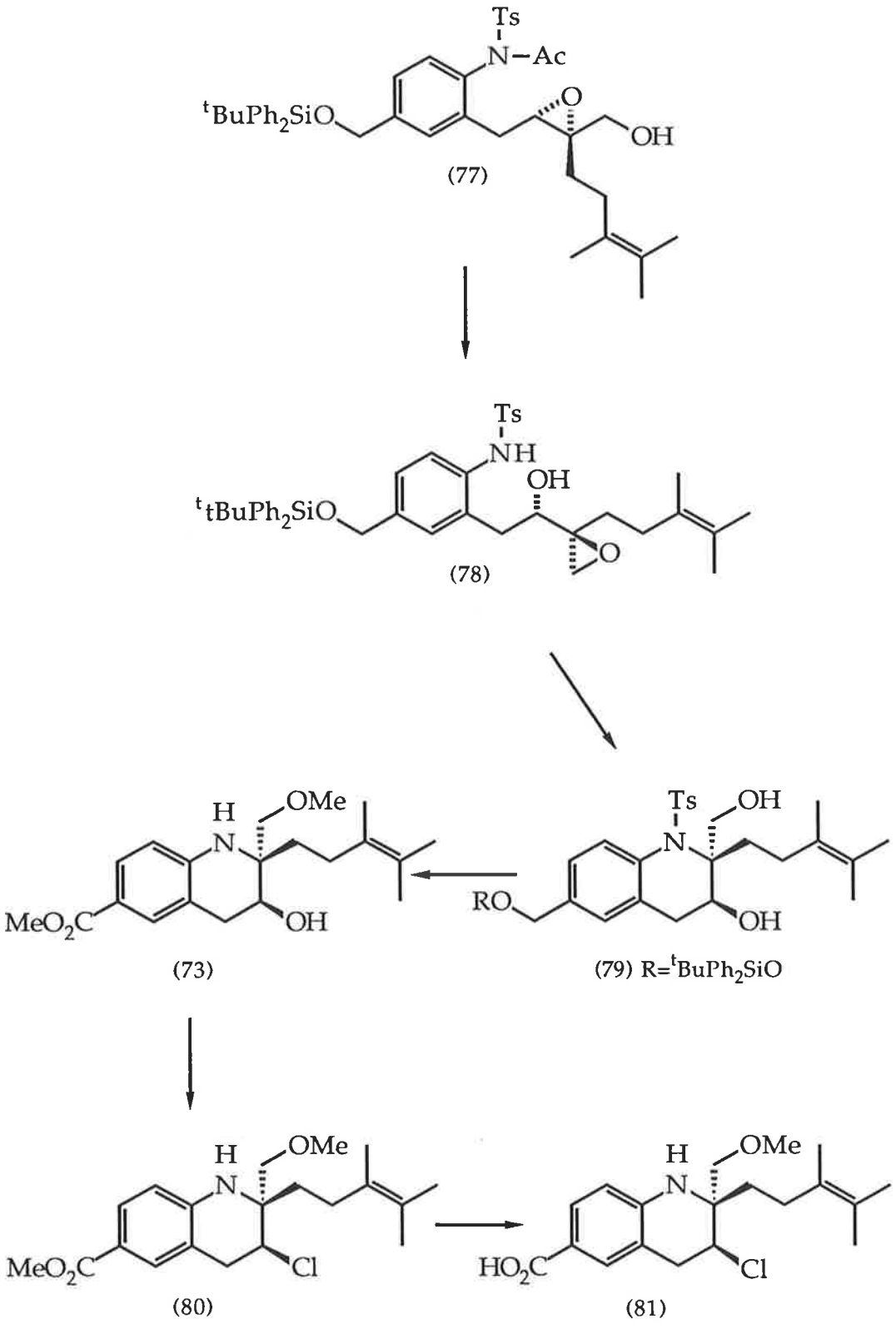


Scheme 23

Ester reduction of (76), followed by sulphonamide group protection and asymmetric epoxidation, led to epoxyalcohol (77) which was in turn converted via multiple steps including another epoxidation, to a single diastereomer of (78). The stereochemistry of (78) was deduced from the configuration of ester (73) (*vide infra*).

The second key step involved cyclization by acid-catalysed intramolecular attack on the epoxide function of (78) with trifluoroacetic acid in toluene to produce (79). This method of cyclization differs from the electrophile-initiated attack on a double bond in our intended synthesis.

The cyclized compound (79) was converted to ester (73) via a lengthy series of protections, deprotections, stepwise oxidation and monomethylation. The relative stereochemistry of (73) was determined by ^{1}H n.m.r. spectral data and n.O.e. experiments to be 2*R*,3*S*, The hydroxyester (73) was converted to chloroester (80) in two steps, using diethyl azodicarboxylate and triphenylphosphine followed by tetraethylammonium chloride with the reaction proceeding via an aziridine with double inversion at C-3. Finally, hydrolysis of (80) yielded (+)-virantmycin (81) whose spectral and chromatographic behaviour was identical with that of natural virantmycin (1). The optical rotation of (81) ($[\alpha]^{24}_D$ +11.2°, c 0.125, $CHCl_3$) was different from that of (1) ($[\alpha]^{24}_D$ –11.1°, c 0.175, $CHCl_3$). The stereochemistry of (81) was assigned on the basis of n.m.r. spectral data and n.O.e. experiments.

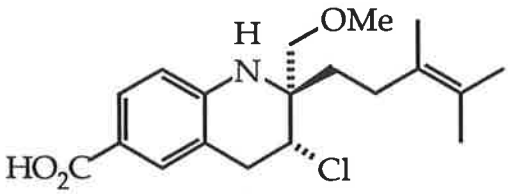

Ts
N–Ac
^{t}BuPh$_2$SiO
O
OH
(77)
Ts
NH
OH
^{t}tBuPh$_2$SiO
O
(78)
H
N
OMe
MeO$_2$C
OH
(73)
Ts
N
OH
RO
OH
(79) R=^{t}BuPh$_2$SiO
H
N
OMe
MeO$_2$C
Cl
(80)
H
N
OMe
HO$_2$C
Cl
(81)

Scheme 24

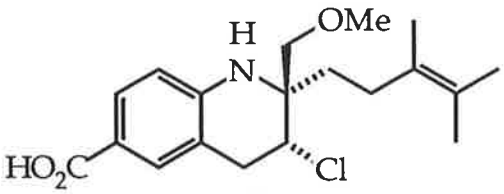
This synthesis of antipodal virantmycin led to a suggestion that the absolute configuration of the natural product is 2*S*, 3*R*, at the two chiral centres[6].

In 1990 Pearce and Sanders[9] determined the stereochemistry of virantmycin by n.O.e. difference spectroscopy to be 2*R*, 3*R*. This reversed the earlier stereochemical proposal for C-2 from Shirahama and co-workers[6].

Shirahama, Matsuda and Morimoto[7,8] reported stereospecific total syntheses of (±)-virantmycin (1) and its diastereomer (±)-(82) in 1991. The methodology employed in these syntheses is again quite different to that in our intended synthesis.

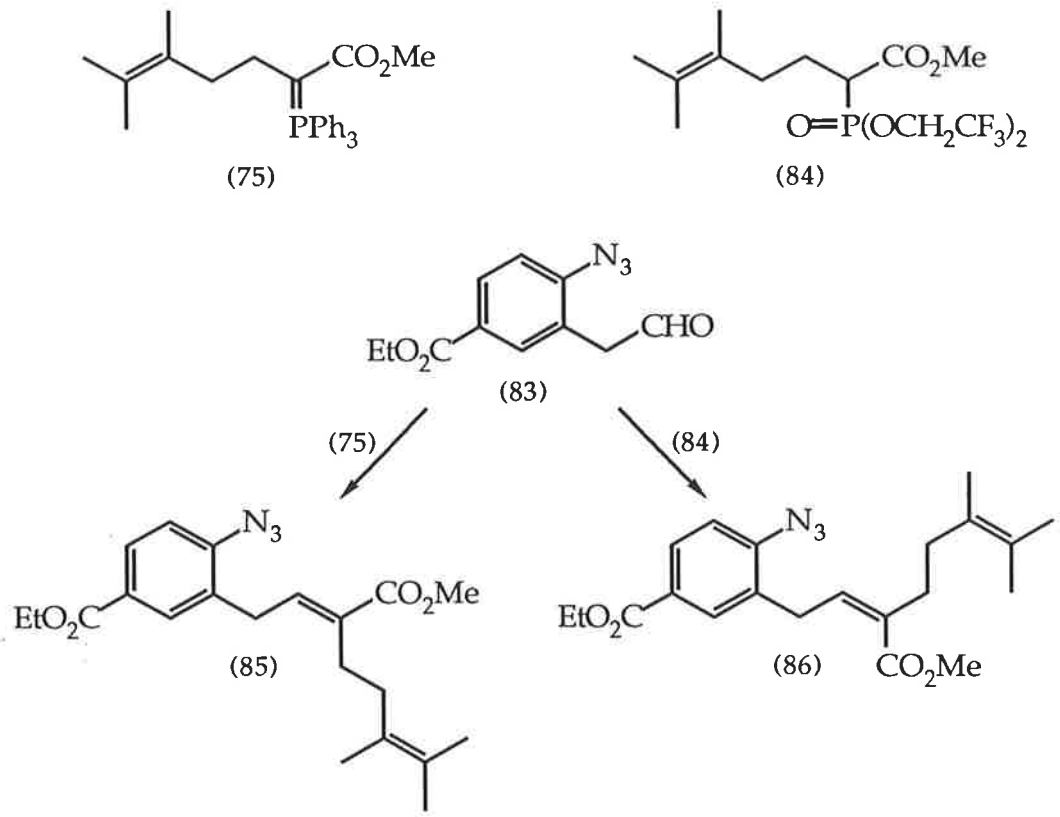


(1)



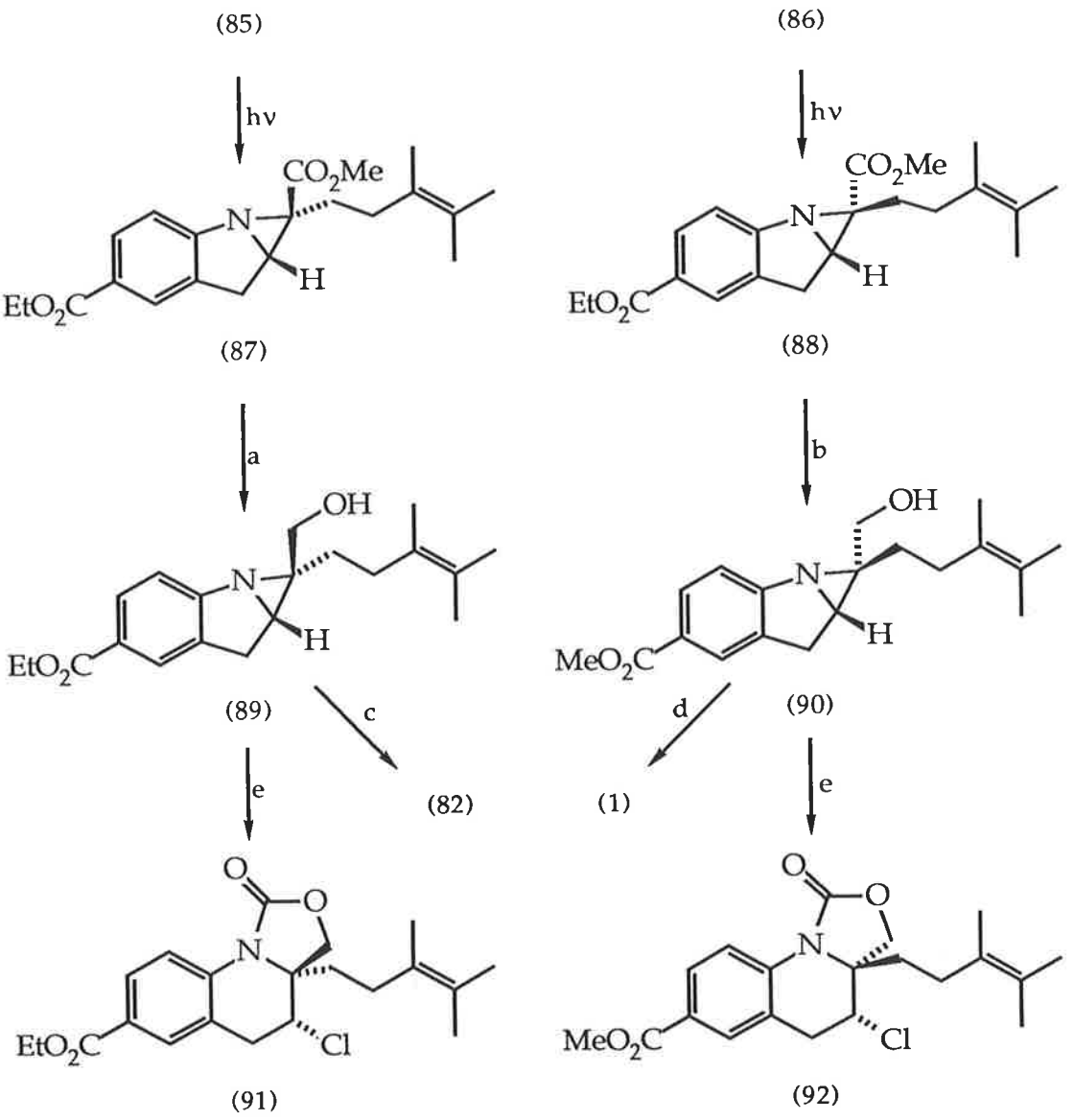
(82)

The first key step was stereoselective olefination of the aldehyde (83). The Wittig reaction of (83) with phosphorane (75) yielded *E*-olefin (85). On the other hand, the Horner-Emmons reaction of (83) with phosphonate (84) provided *Z*-olefin (86) (Scheme 25).



Scheme 25

The second key step was the intramolecular nitrene-addition reaction by photolysis of (85) and (86) which proceeded with complete stereospecificity to afford aziridines (87) and (88), respectively. Selective reduction of the ester moiety on the aziridine ring of (87) and (88) gave alcohols (89) and (90), respectively (Scheme 26). After methylation of (89) and saponification, highly regioselective ring opening of the aziridine with inversion gave only (±)-(82) which had different chromatographic and spectroscopic properties from the natural product. Following the same sequence of reactions, the synthesis of (±)-(1), identical with the natural product in all chromatographic and spectroscopic properties, was accomplished from (90) (Scheme 26).



a=$LiAlH(O^tBu)_3$ c=(1)NaH/Bu_4NI d=(1)KH, (2)MeI
b=(1)$LiAlH_4$, (2)MnO_2 (2)MeI, (3)NaOH (3)NaOH, (4)Et_4NCl/TFA
(3)KCN/MnO_2 (4)Et_4NCl/TFA e=(1)Et_4NCl/TFA
(2)Im_2CO

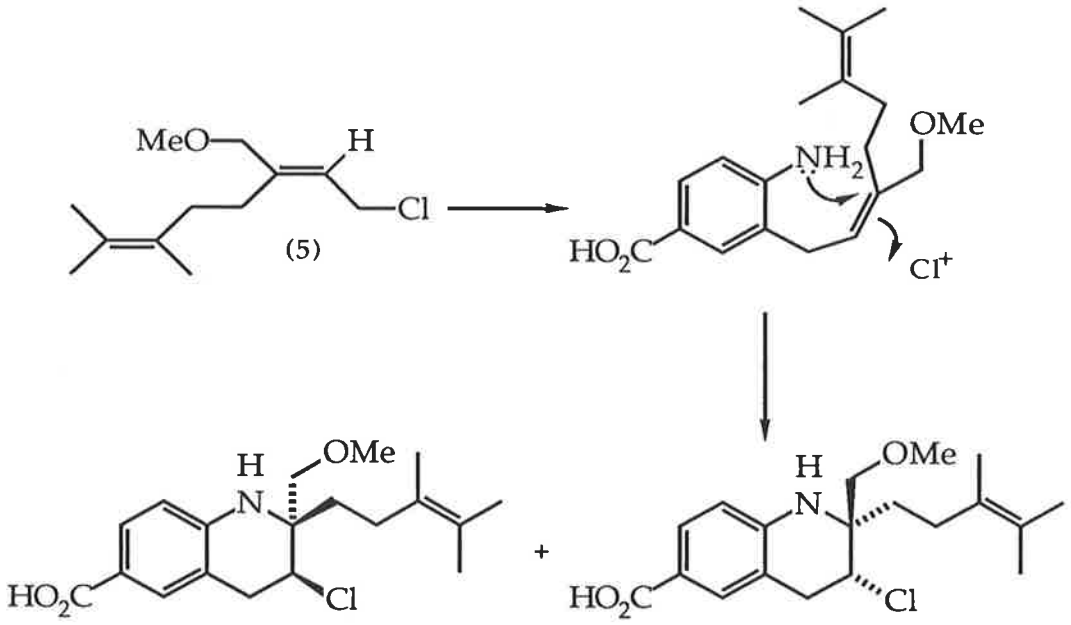
Scheme 26

The relative stereochemistry of compounds (82) and (1) was unambiguously assigned from n.O.e. experiments with (91) and (92) which were derived from (89) and (90), respectively (Scheme 26). These results led Shirahama and his

co-workers to the conclusion that the stereochemistry at the two chiral centres of (1) is 2*R*, 3*R*[8], in agreement with the Cambridge assignment[9].

At the time of commencement of our work, the stereochemistry at C-2 and C-3 of virantmycin was unknown. Our synthetic strategy was therefore designed to be not only general (in order to prepare a range of virantmycin analogues) but also to enable streochemical control, which would perhaps have led to an assignment of the stereochemistry of the natural product. Stereochemical control should be possible for two reasons. Firstly, the allylic subunit (5), planned to be prepared as in Scheme 2, should have known geometry by virtue of the stereoselectivity of Grignard addition to the alkyne. It is therefore expected that the allylbenzene species (3) will also be of known geometry. Secondly, electrophile-initiated cyclization of (3) is expected to have the nitrogen to C-2 bond and C-3 to chlorine/electrophile bond forming *anti* to each other, resulting in a product consisting of a single diastereomer. Access to the individual stereoisomers of the cyclized product may be possible using methods of chiral induction, perhaps by affixing a chiral auxiliary to the nitrogen before the cyclization process.

If the electrophile initiated cyclization of (3) does proceed in the expected manner (with the new bonds forming *anti* to each other) the diastereomer produced would be that shown in Scheme 27 below.



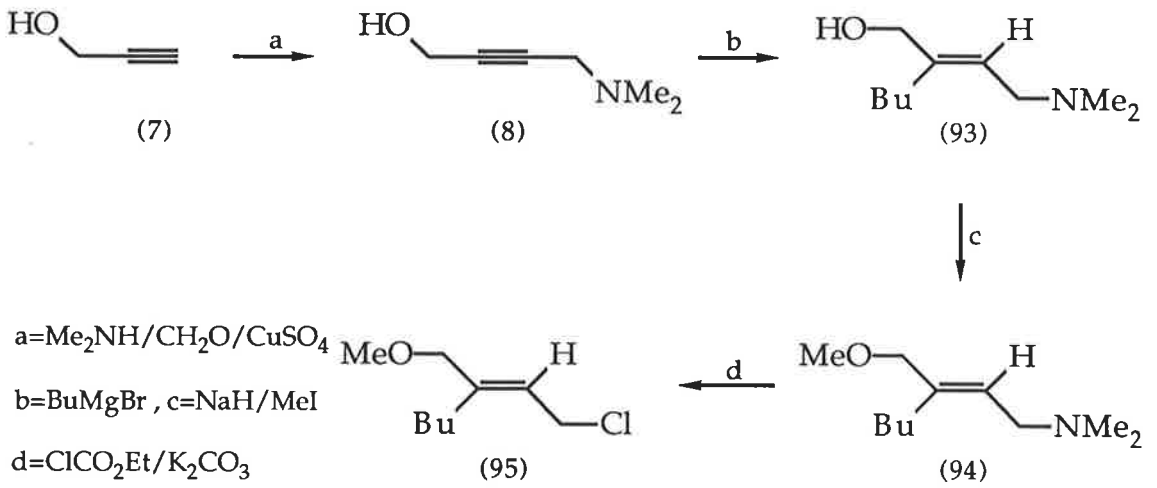
Scheme 27

With the benefit of knowledge of the recent n.O.e. studies at Cambridge[9] and Sapporo[8], it can be seen that this diastereomer would have different stereochemistry to that of the natural product, although it was not possible to know this at the time of designing the approach.

CHAPTER 1

In order to establish the conditions for synthesis of the allylic virantmycin subunit (5) via the sequence of reactions outlined in Scheme 2, butylmagnesium bromide was used as a model. The reason for this was to minimize wastage (4 equivalents are used) of the bromide precursor to the pentenyl Grignard reagent required for synthesis of (5), since it was not readily available and had to be prepared by a multi-step synthesis.

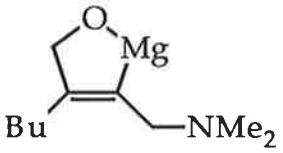
The most efficient order of carrying out the steps in Scheme 2 was investigated. The first variation studied, using the model system, was that shown in Scheme 28 below.



Scheme 28

The aminobutynol (8) was easily prepared from propargyl alcohol (7) using a reported procedure[15]. Conversion of (8) to (93) was achieved in 90% yield by reaction with 4 equivalents of butylmagnesium bromide in ether at room

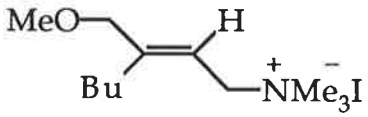
temperature. Only one isomer was produced according to the spectral data* , presumably the *E* isomer, in accordance with the *anti* addition of Grignard reagents to triple bonds described in analogous reports previously [12,13,20]. The formation of only the *E* isomer in this type of reaction has been rationalized by the proposed existence of a vinylmagnesium intermediate[12,20], such as that shown below.



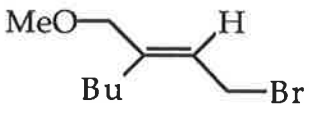
Methylation of (93) to produce (94) proved difficult and numerous attempts met with little success. Reaction of the alcohol (93) with 1.5 equivalents of sodium hydride and then 1.1 equivalents of iodomethane in an ether/dimethylformamide mixture returned mainly starting material with a small amount of the methylated product since a singlet due to the methoxyl group at δ 3.3 and a singlet at δ 3.85 due to the methylene group adjacent to oxygen in the ^{1}H n.m.r. spectrum and a molecular ion peak at *m/z* 185 in the mass spectrum were observed. It was noted that the sodium alkoxide salt of (93) was only slightly soluble in ether, so a small amount of dimethylformamide was added in an attempt to make the mixture homogeneous. This was only partially successful, even after raising the temperature to reflux.

*For the vast majority of compounds prepared from the work described in this thesis, the spectral data obtained was that expected from the structures. For this reason, detailed discussion of spectral data has been minimized in the Results and Discussion section. Full, interpreted, spectral data is detailed in the Experimental section.

In an attempt to increase the alkoxide ion solubility, the reaction was repeated using tetrahydrofuran as solvent and excess of iodomethane was used. This resulted in a more homogeneous reaction mixture and reaction at room temperature for 24 h resulted in overmethylation, producing the quaternary ammonium salt (96) .



(96)



(97)

An analogous reaction carried out using dimethyl sulphoxide as solvent also resulted in formation of (96).

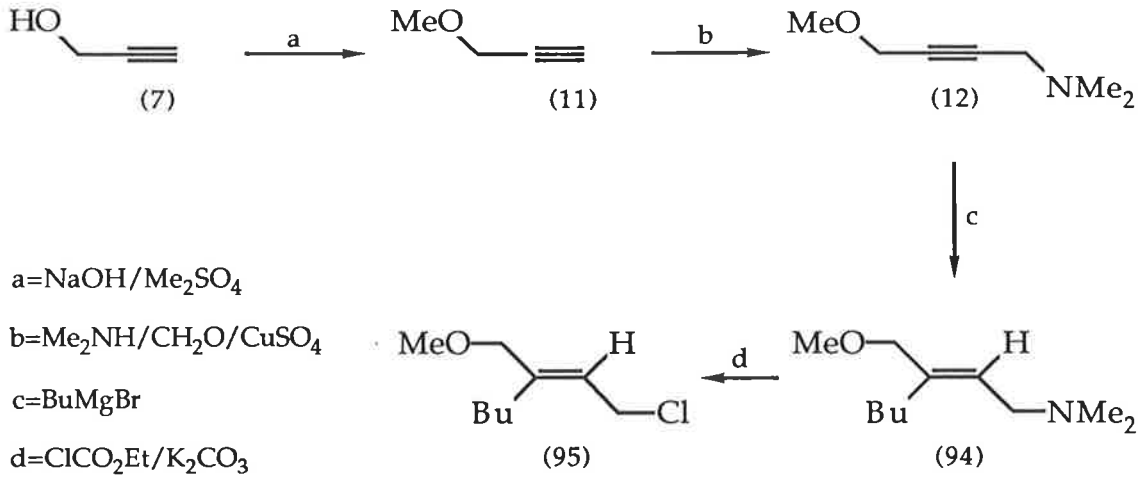
Having obtained the salt (96), the displacement of the trimethylamino moiety with bromide ion to produce (97) was investigated. Reaction of (96) with lithium bromide in acetone (lithium chloride is not soluble) did not produce the desired product (97), even after heating under reflux for 2 days. The starting material (96) was recovered.

Attention was then directed towards methylation of the lithium alkoxide salt of (93). Deprotonation of (93) was achieved with ethereal methyllithium at 0-5° and the resulting lithium salt was subsequently reacted with 1.1 equivalents of iodomethane in ether at 0-5° for 1 h. ^{1}H n.m.r. spectoscopic analysis of the product revealed that only starting material had been recovered, again suggesting the low solubility of the alkoxide ion inhibits the methylation reaction.

It has been reported that alcohols can be methylated with diazomethane under catalysis by Lewis acids, for example boron trifluoride etherate[21], fluoroboric acid[22] or silica gel[23]. When alcohol (93) was treated with excess of ethereal diazomethane[24] in the presence of two molar equivalents of boron trifluoride etherate in ether at 0-5° overnight, only starting material was recovered, as indicated by the ^{1}H n.m.r. spectrum.

The use of silica gel as catalyst was also investigated since a variety of alcohols have been methylated with diazomethane catalysed by ten to one hundred weight equivalents of silica gel[23]. Treatment of (93) with excess of ethereal diazomethane[24] in the presence of ten weight equivalents of silica gel in ether at room temperature overnight achieved approximately 50%*O*-methylation according to relative integration of the singlets in the ^{1}H n.m.r. spectrum corresponding to the methylene group adjacent to the oxygen atom in (93) and (94), perhaps indicating that silica gel methylation is competitive with methylation of the alcohol (93).

Since the methylation of (93) proved not to be straightforward, it was decided to try a variation in the order of the conversions outlined in Scheme 2, still using the butyl model system, where propargyl alcohol was methylated before carrying out the Mannich aminomethylation reaction (Scheme 29). In this variation, the problem of *N*-methylation accompanying desired *O*-methylation is avoided.



Scheme 29

The methoxypropyne (11) was readily prepared from propargyl alcohol (7) using a reported procedure[25]. Aminomethylation of (11) to produce (12) was achieved in good yield after modifying the procedure of Salvador and Simon[15] by using methanol as cosolvent. This was required to solubilize the substrate in the reaction mixture. Also an extended reaction time, relative to propargyl alcohol, was required for the methylated compound.

The Grignard addition reaction of the methoxyamimobutyne (12) required considerably more vigorous conditions than those for the aminobutynol (8). Production of (94) in 52% yield required reaction of (12) with 2.5 equivalents of butylmagnesium bromide in refluxing benzene for 7 h. Only one isomer of (94) (presumably *E* as before) was observed according to the spectral data, again consistent with literature data[12,13,14,20]. Reaction with 4 equivalents of Grignard reagent did not improve the yield. The less vigorous conditions of stirring with 4 equivalents of Grignard reagent in (a) ether at room temperature for 22 h, (b) ether with heating under reflux for 30 h, (c) tetrahydrofuran at room temperature for 3 h, or (d) tetrahydrofuran with

heating under reflux for 12 h, resulted in isolation of essentially starting material only.

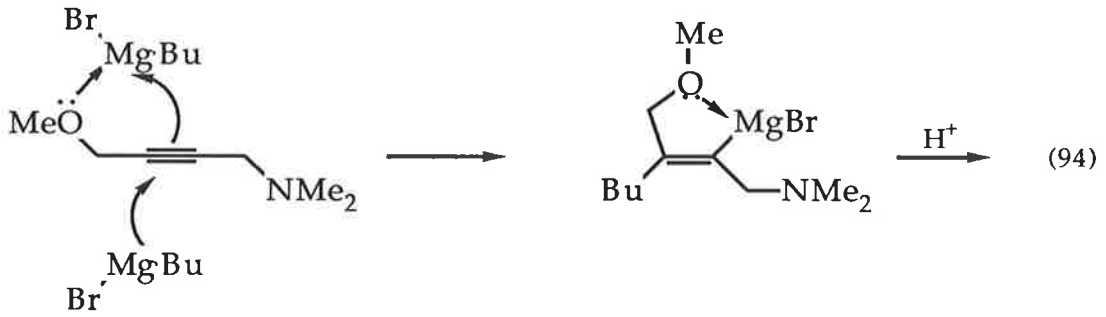
Mornet and Gouin have reported that in reactions of alkoxyaminobutynes with Grignard reagents (2 molar equivalents) in benzene or ether, a significant proportion of allene by-product (resulting from addition of the Grignard reagent to the other end of the triple bond followed by elimination of an alkoxide ion) is produced[14]. We did not observe the expected by-product (98) (Scheme 30) in our reaction which was carried out under similar conditions.

Scheme 30

The desired Grignard addition product was obtained in superior yield to the yields reported by Mornet and Gouin[14] from analogous reactions.

The only cases where the allene (98) was observed occurred when a lower proportion of Grignard reagent (1.3 molar equivalents) was used. Reaction of (12) with 1.3 equivalents of butylmagnesium bromide in refluxing benzene for (a) 90 min and (b) 7 h, gave products corresponding by infrared and ^{1}H n.m.r. spectroscopy to starting material (12), desired product (94) and the allenic by-product (98) in the ratios 3 : 1.5 : 1.25 for (a) and 1.5 : 2 : 1.9 for (b), since in addition to the infrared absorptions and ^{1}H n.m.r. signals due to (12)

and (94), an absorption at 1960 cm^{-1} in the infrared spectra and multiplets at δ 2.9 and 4.7 plus a singlet at δ 2.2 in the ^1H n.m.r. spectra were also observed. Presumably, the allene forms under these conditions because addition of the butyl group to the "nitrogen-end" of the triple bond becomes more favourable since there is no second equivalent of Grignard reagent present to direct attachment selectively to the "oxygen-end" (Scheme 31).



Scheme 31

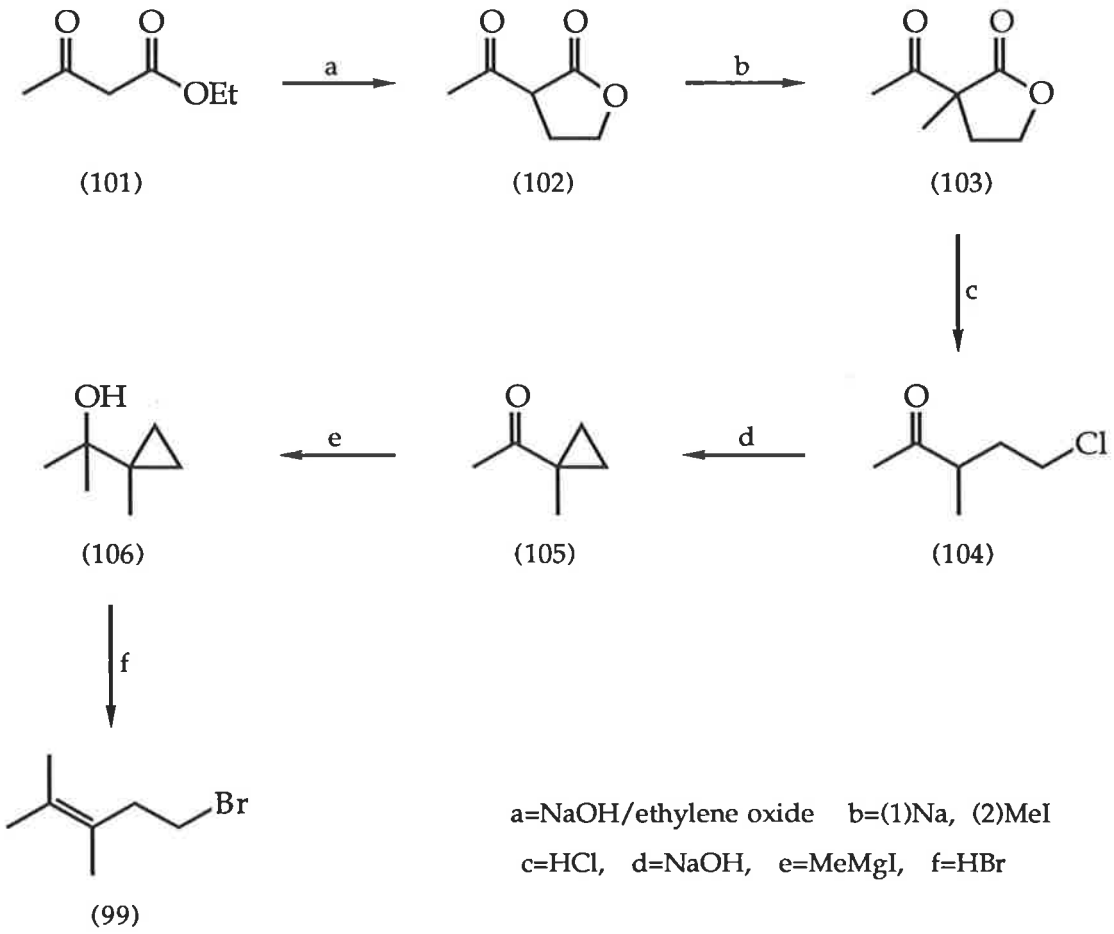
It is known that allylic tertiary amines can be easily converted to allylic chlorides by reaction with excess of ethyl chloroformate and that this conversion does not affect the stereochemistry of the double bond[13]. Amines closely structurally related to (94) had been used in this reaction so we adopted the literature procedure[13] for our case. Reaction of (94) with a ten-fold excess of ethyl chloroformate in benzene afforded the chloride (95) in 81% yield.

The successful synthesis of model compound (95) meant that the methodology for preparation of virantmycin precursor (5) had been established. Attention could now be directed towards the actual synthesis of (5).

A necessary preliminary in this synthesis was the preparation of compound (99) which is the bromide precursor to the required Grignard reagent (100).

(99) (100)

The synthetic scheme used to prepare bromide (99)[26] was that shown in Scheme 32.



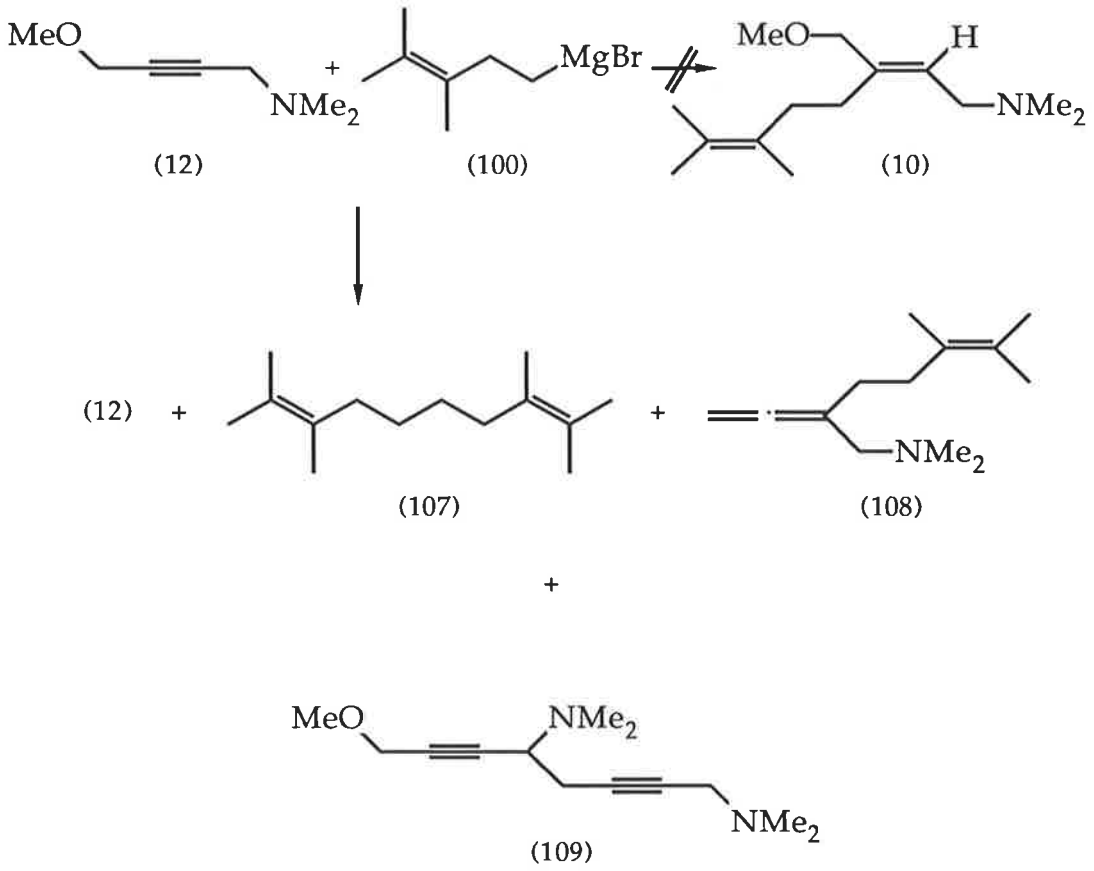
Scheme 32

Ethyl acetoacetate (101) was converted to the lactone (102) by a modification of the procedure of Johnson[27]. Methylation of (102) to produce (103) was achieved by a modification of the procedure of Stepanov and Smirnov[28]. Decarboxylation of (103) to produce the chloroketone (104) and its subsequent cyclization to give the cyclopropyl ketone (105) were carried out by adapting a literature procedure[29]. Treatment of (105) with 1.5 equivalents of methylmagnesium iodide in refluxing ether for 2 h provided the carbinol (106)[26] which, in dichloromethane solution, was shaken with excess of concentrated hydrobromic acid[26] for 5 min to give the desired bromide (99).

Having obtained the bromide (99), the synthesis of virantmycin precursor (5) as outlined in Scheme 2 could be commenced. Treatment of the methoxyaminobutyne (12) with 2.5 equivalents of Grignard reagent (100) in refluxing benzene for 7 h did not produce the desired alkene (10); instead, a mixture of four products, two major and two minor, were obtained. T.l.c. analysis indicated a non-polar component (high R_F) and a polar component (low R_F), which were separated by chromatography. The high R_F component was the hydrocarbon (107) resulting from dimerization of the Grignard reagent. The low R_F component consisted mainly of starting alkyne (12) together with two minor components, one of which appeared to be the allene (108) since an absorption at 1960 cm^{-1} in the infrared spectrum, a singlet at δ 1.65 integrating for nine protons, multiplets at δ 2-2.5 and 2.15 integrating for two protons each, a singlet at δ 2.3 (NMe_2), a multiplet at δ 2.95 integrating for two protons and a multiplet at δ 4.75 (terminal allene CH_2) in the ^1H n.m.r. spectrum and a peak at m/z 193 in the mass spectrum, all of which could be attributed to this structure, were observed. The other minor product was probably the alkyne dimer (109) since a peak at m/z 224 in its mass

spectrum was observed. Accurate mass determination revealed that the peak corresponded to $C_{13}H_{24}N_2O$ which could have resulted from a M+2 ion from (109) (both amine groups protonated).

Repeat reactions using either benzene or ether as solvent with variations in reaction time, provided the same product mixture.

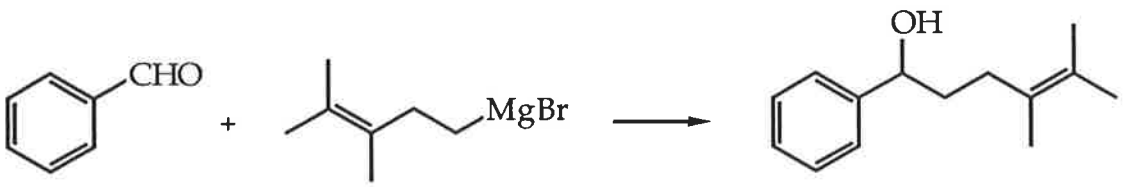


Scheme 33

From these results, it appeared as though either Grignard reagent formation was not efficient or dimerzation of the Grignard reagent was a competitive reaction pathway to the addition to the triple bond. Assuming the latter, with

the aim of making addition the more favourable pathway, Grignard reagent formation was attempted with the substrate alkyne (12) already present in the ethereal mixture. This might enable immediate reaction with the alkyne on Grignard formation. Refluxing the mixture for 5.5 h resulted, after workup, in starting materials, alkyne (12) and bromide (99) being recovered, indicating unsuccessful Grignard reagent formation.

In order to confirm satisfactory formation of the Grignard reagent (100), reaction with a reactive carbonyl compound was carried out. Reaction of benzaldehyde with 1.2 equivalents of (100) in refluxing ether for 30 min provided the expected product alcohol (110) in good yield (Scheme 34). The Grignard dimer (107) was detected as a minor component in the crude product of this reaction.

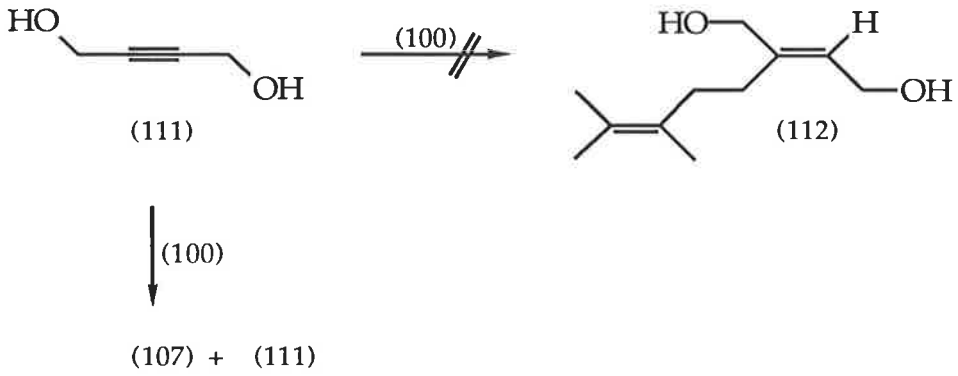


(100) (110)

Scheme 34

The success of this reaction prompted investigation of reaction (100) with alkyne substrates more reactive than methoxyaminobutyne (12). Grignard reagents are known to add to the triple bond of but-2-yn-1,4-diol (111)[20], so it was decided to study this reaction using (100). Treatment of the diol (111) with 4 equivalents of (100) in a refluxing ether/tetrahydrofuran mixture for

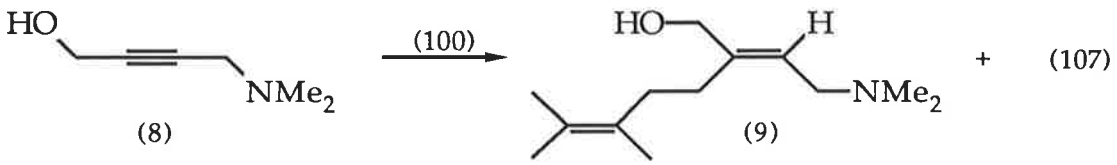
4 h resulted in recovery of (111) plus the Grignard dimer (107). None of the desired product (112) was detected (Scheme 35).



Scheme 35

This result implies that a more reactive alkyne substrate is required.

Since hydroxyaminobutyne (8) reacted with butylmagnesium bromide to produce (93) in high yield under mild conditions, it was decided to try this substrate in a reaction with (100). Reaction of alkyne (8) with 4 equivalents of Grignard reagent (100) in ether at room temperature for 5 h resulted in good yield of the desired product (9) plus a significant amount of dimerized Grignard reagent (107) (Scheme 36). These two compounds were easily separated by fractional distillation.



Scheme 36

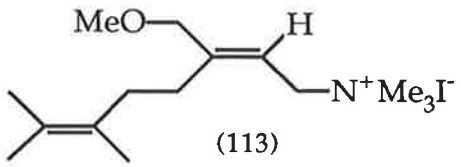
Since the bromide precursor to Grignard reagent (100) was prepared via a multi-step synthesis, the use of 4 molar equivalents of (100) in conversion of (8) to (9) makes this a rather inefficient step. One equivalent of Grignard reagent is consumed in deprotonation of the hydroxyl group and other equivalent may be consumed in complexation to the amino moiety of (8) and it was thought that if a readily available Grignard reagent such as methylmagnesium iodide, for example, was used for this purpose, the efficiency of the step would be improved. This idea was investigated by employing butylmagnesium bromide as a model for (100).

Deprotonation of (8) was effected by addition of an ethereal solution of (8) to 1.1 equivalents of methylmagnesium iodide in ether. Addition of the resulting alkoxide mixture to an ethereal solution of 1.3 equivalents of butylmagnesium bromide and subsequent reaction at ambient temperature for 17 h resulted in a mixture comprising the desired product (93) and the starting material (8) in the ratio 3:5 as indicated by integration of the ^{1}H n.m.r. spectrum. An analogous reaction using 2.2 equivalents of methylmagnesium iodide and 1.3 equivalents of butylmagnesium bromide provided a mixture of (93) and (8) in the ratio of 5:7. Repetition of this reaction with the modification of using 2.5 equivalents of butylmagnesium bromide returned a product mixture consisting of (93) and (8) in the ratio 18:5.

These results suggested that a large excess of Grignard reagent was necessary to achieve total conversion of (8) to (93), hence it was decided to return to the initial procedure of using 4 molar equivalents.

In the light of the inability to effect selective *O*-methylation of compound (93) (see earlier), it was anticipated that a similar transformation of compound (9) would present difficulties. However, in order to proceed with Scheme 2, it was necessary that this problem be overcome.

The methylation of (9) was investigated. The first method used was deprotonation of the hydroxyl group with sodium hydride and subsequent reaction of the alkoxide with 1.1 equivalents of iodomethane in tetrahydrofuran at room temperature. The product of this reaction gave a poorly resolved ^{1}H n.m.r. spectrum, indicating some decomposition, but it showed an allylic methyl group singlet resonance at δ 1.65, an allylic methylene group multiplet at δ 2.05-2.45, a methoxyl group singlet at δ 3.45, a singlet at δ 3.55 due to a trimethylamino moiety, a singlet at δ 4.0 due to a methylene group adjacent to an oxygen atom, a doublet at δ 4.25 corresponding to a methylene group adjacent to a positively charged nitrogen atom and a triplet in the vinyl proton region at δ 5.7. The mass spectrum showed a peak at *m/z* 240. This data indicated that the quaternary ammonium salt (113), from overmethylation, had formed as was the case with the butyl model system earlier.



(113)

The second method used was deprotonation with ethereal methyllithium at 0-5° and subsequent reaction of the alkoxide with 1.1 equivalents of

iodomethane in ether at 0-5°. Quenching of the reaction mixture and workup resulted in starting material (9) being recovered, which was also the case with the butyl model system earlier.

It has been reported that in the methylation of aminoalcohols of the type (114) with dimethyl sulphate in tetrahydrofuran, predominant *O*-methylation can be achieved when sodium hydride is used as the base[30]. When lithium hydride, calcium hydride, methyllithium, methylmagnesium iodide or no base is used, exclusive *N*-methylation occurs[30]. No explanation has been proposed[30].

$$RNH(CH_2)_nOH \qquad n=2,3$$

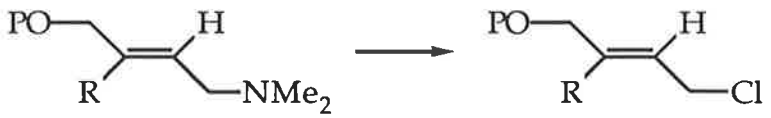
(114) R=H,Me

It was therefore decided to use the sodium hydride/dimethyl sulphate method for our system. Deprotonation of aminoalcohol (9) with a suspension of sodium hydride in tetrahydrofuran followed by reaction with dimethyl sulphate for 1 h provided a mixture of three products according to spectral data. The ^{1}H n.m.r. spectrum of the crude product showed resonances corresponding to starting alcohol (9) and resonances attributable to quaternary ammonium salt (113). The ^{1}H n.m.r. spectrum also showed a singlet at δ 3.3 due to a methoxyl group and a singlet at δ 3.8 due to a methylene group adjacent to an oxygen atom. The microdistilled product gave a ^{1}H n.m.r. spectrum identical to that of the crude product, except the signals attributed to the salt (113) were missing. The mass spectrum showed a peak at *m/z* 225. The data implies that the distilled sample consisted of a mixture of starting alcohol (9) and desired product (10) in approximately equal

proportions as indicated by integration of the methylene group adjacent to oxygen signals in the ^1H n.m.r. spectrum. The reaction was repeated with the modification of halving the molar equivalents of dimethyl sulphate, since in principle each molecule can donate two methyl groups. This reaction provided a similar product mixture.

The continual problem of competitive *O*- and *N*-methylation with the aminoalcohol (9) led to abandoment of the methylation reaction. It was decided to protect the hydroxyl group of (9) as a silyl ether, convert the amino group to a chloro moiety (using ethyl chloroformate as before) and couple the resulting allylic chloride to the *N*-protected aromatic subunit. Subsequent removal of the silyl protecting group should enable selective *O*-methylation to be achieved since there would be no amino group in competition. The two silyl protecting groups considered were the trimethylsilyl (TMS) and *tert*-butyldimethylsilyl (TBDMS) groups.

The alcohol (9) was converted to the corresponding TMS ether (115)[31] in 88% yield and to the corresponding TBDMS ether (116)[32] in 93% yield for use in carbonochloridate cleavage reactions to produce the corresponding silyl protected allylic chlorides (117) and (118) respectively (Scheme 37).



(115) P=TMS
R=$(CH_3)_2C=C(CH_3)CH_2CH_2$

(116) P=TBDMS
R=$(CH_3)_2C=C(CH_3)CH_2CH_2$

(119) P=TBDMS , R=Bu

(117) P=TMS
R=$(CH_3)_2C=C(CH_3)CH_2CH_2$

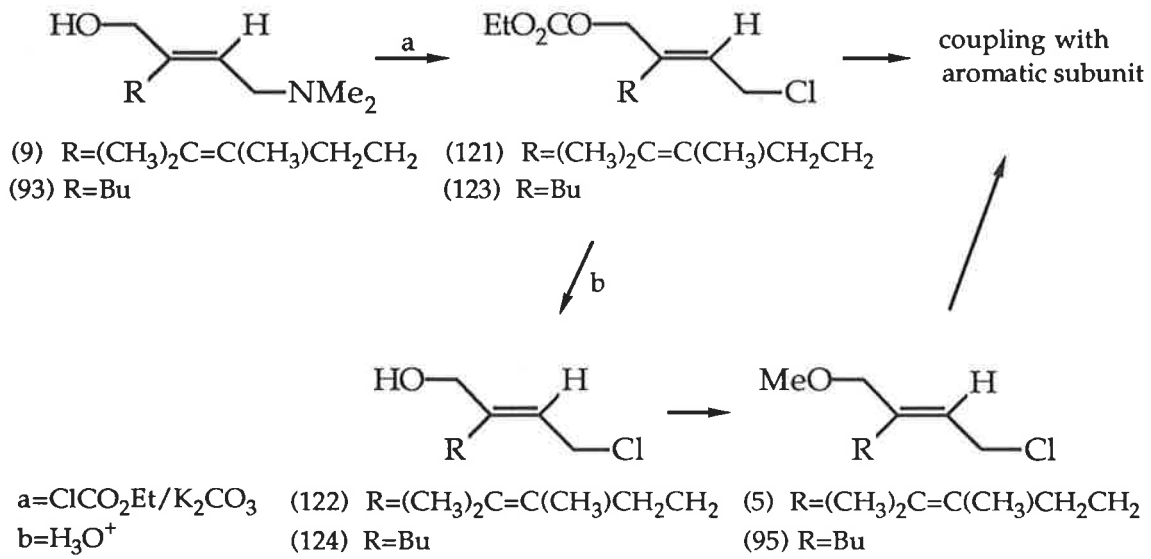
(118) P=TBDMS
R=$(CH_3)_2C=C(CH_3)CH_2CH_2$

(120) P=TBDMS , R=Bu

Scheme 37

In order to avoid wastage of the silyl ethers (115) and (116), the butyl model compound (119) was prepared analogously, in 98% yield. Subsequent treatment of (119) with a ten-fold excess of ethyl chloroformate in benzene provided the chloride (120).

An alternative to the silyl protection step as a means of solving the methylation problem might be to use the unprotected aminoalcohol (9) in the cleavage reaction. This should produce the allylic chlorocarbonate (121) (Scheme 38) resulting from nucleophilic attack of the hydroxyl group (as well as the amino group) on ethyl chloroformate. Compound (121) could then be coupled with the *N*-protected aromatic subunit (assuming the carbonate function is stable to the cuprate reaction conditions), the carbonate group later removed by hydrolysis and then *O*-methylation carried out. Alternatively, (121) could be hydrolysed to the hydroxy choride (122) which could then be methylated to produce (5) for coupling to the aromatic subunit (Scheme 38).



Scheme 38

To avoid wastage of the side chain bromide (99), the butyl model compound (93) was used to investigate the reactions outlined in Scheme 38. Conversion of (93) to the chlorocarbonate (123) was achieved by treatment with a ten-fold excess of ethyl chloroformate in benzene.

Having successfully synthesized a range of model allylic subunits, a study of their coupling to the aromatic subunit and subsequent cyclization reactions could now be undertaken.

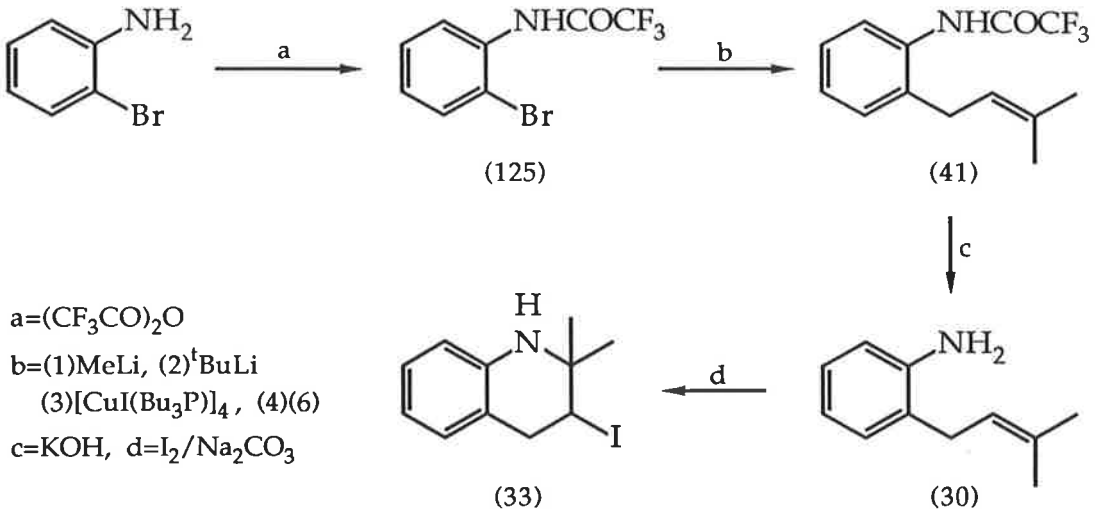
CHAPTER 2

The synthesis of aromatic virantmycin subunit (16) was achieved using the chemistry devised by Raner[10] (Scheme 3). Conditions for the coupling and cyclization reactions were established using simple model compounds. As Raner[10] had done earlier, trifluoroacetamide (125) and 3,3-dimethylallyl bromide (6) were the compounds chosen for this purpose.

Compound (125) was prepared by modifying the procedure of Raner[10]. Coupling with (6) was achieved using the method of Raner[10] by treating (125) in tetrahydrofuran solution at −50° sequentially with 1 equivalent of methyllithium to remove the amide (NH) proton, 2 equivalents of *tert.*-butyllithium to form the aryllithium species, 1 equivalent of *tetrakis*[iodo(tributylphosphine) copper(I)][33] to form the arylcuprate species and finally (6) for 5 min to produce the allylbenzene (41).

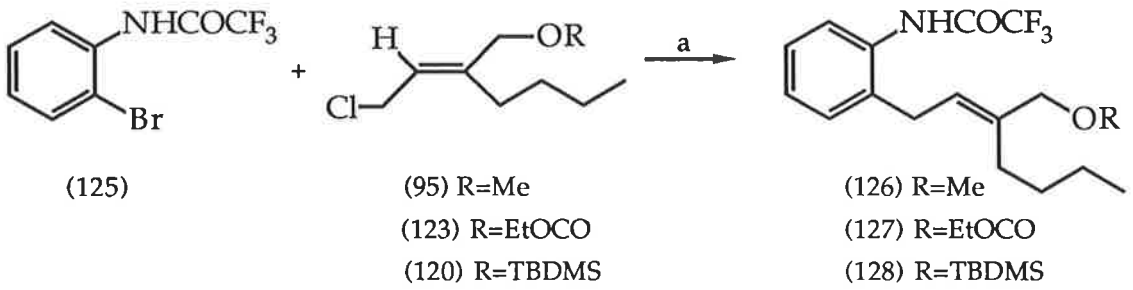
Methyllithium does not undergo lithium-bromine exchange[10], so use of this reagent first, followed by *tert.*-butyllithium results in the problems of deprotonation competing with lithium-bromine exchange being avoided. If this competition were to occur, metallation would proceed whilst there are still acidic hydrogens in solution and this would lead to protonation of the newly formed aryllithium species[10].

The amide (41) was hydrolysed with potassium hydroxide in methanol to give the free amine (30). Cyclization of (30) to the iodotetrahydroquinoline (33) was achieved by the procedure of Raner[10] using iodine as the electrophile (Scheme 39).



Scheme 39

The allylic chlorides (95), (120) and (123) represent closer models to (5) than (6) since they contain much larger groups attached to the alkene carbon that is attacked by the amino group in the cyclization reaction. The coupling of these compounds to aromatic subunits was investigated (Scheme 40).



a=(1)MeLi, (2)^{t}BuLi, (3)[CuI(Bu$_3$P)]$_4$, (4)(95) or (123) or (120)

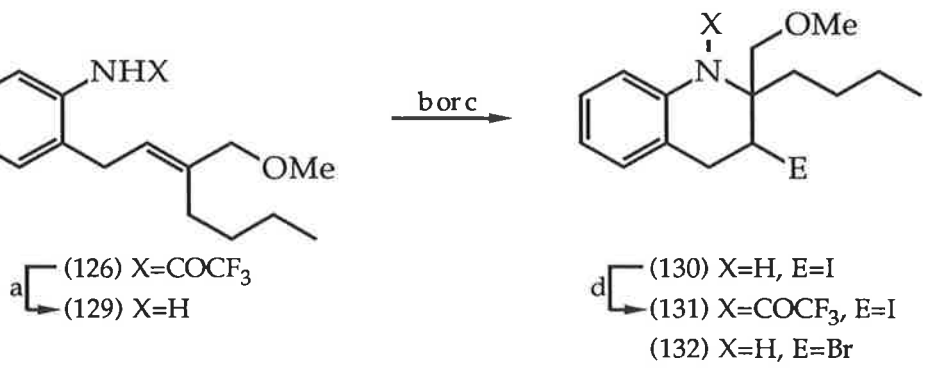
Scheme 40

The aryl cuprate species of (125), prepared by the procedure described above[10], underwent reaction with chloride (95) in tetrahydrofuran at −50° to give the

allylbenzene (126) . Analogous reactions using allylic chlorides (123) and (120) afforded the allylbenzenes (127) and (128), respectively.

These results showed that an aryl cuprates species can be efficiently coupled with allylic chlorides to produce allylbenzenes and that the reaction is tolerant of a variety of functional groups.

The applicability of Raner's iodine initiated cyclization method[10] to these systems was initially tested with compound (129) (Scheme 41).



a=KOH, b=I_2/Na_2CO_3, c=Br_2/Na_2CO_3, d=$(CF_3CO)_2O$

Scheme 41

Treatment of (129) with 1 equivalent of iodine and sodium carbonate in dichloromethane for 4 h according to the procedure of Raner[10] resulted in an intractable product mixture as evidenced by t.l.c. and a poorly resolved ^1H n.m.r. spectrum. The reaction was repeated in darkness in order to minimize any possible, radical, side reactions but this too resulted in an intractable product mixture. A further repetition of the reaction with 2 equivalents of iodine in darkness again afforded the same outcome.

It was concluded that perhaps the reaction conditions were too harsh, so a reaction was carried out at lower temperature and over a shorter time span. The allylaniline (129) was treated with 2 equivalents of iodine and sodium carbonate in dichloromethane at 0° for 30 min. This returned starting material.

These results could suggest that an intermediate set of reaction conditions may enable isolation of the desired tetrahydroquinoline (130) and, accordingly, a reaction was carried out on (129) with 2 equivalents of iodine and sodium carbonate in dichloromethane at room temperature in darkness for 1 h. Again an intractable mixture was obtained.

Raner had reported earlier that iodotetrahydroquinoline (33) was unstable to distillation[10], so it was possible that the desired product (130) in the above reactions was thermally unstable and that cyclization was occurring but the cyclized product was decomposing during attempts to isolate it from the reaction mixture. It was thought that conversion of the iodotetrahydroquinoline to the corresponding trifluoroacetamide (131) (Scheme 41) *in situ* may confer extra stability to the molecule, thus enabling its isolation, assuming of course that cyclization does occur. To this end, another reaction was carried out on (129) using the initial procedure, then adding excess of trifluoroacetic anhydride and allowing the reaction mixture to stir for a further 1 h in darkness before workup.

Flash chromatography of the product from this reaction yielded four fractions. The component of highest R_F was impure and in low yield but showed ^1H n.m.r. spectral characteristics expected of the desired product (131).

These included a doublet of doublets at δ 4.6 attributable to the proton geminal to the iodine atom and coupled with the benzylic methylene protons, a strong methoxy singlet resonance at δ 3.35, a doublet at δ 3.5 attributable to the benzylic methylene protons, a set of aromatic signals very similar in appearance to those of compound (33) (which has the desired iodotetrahydroquinoline skeleton) and the absence of allylic methylene and vinylic proton resonances. The mass spectrum showed a strong molecular ion at *m/z* 455, the value expected for (131). Another fraction of lower R_F corresponded by t.l.c. and ^1H n.m.r. spectroscopy to (126), resulting from trifluoroacetylation of the starting material. The other two fractions showed poorly resolved infrared and ^1H n.m.r. spectra, indicating complex mixtures of products. Considerable baseline material was also observed, suggesting that a significant amount of decomposition was occurring.

Although the desired product (131) did appear to form in this reaction, the yield was very poor and a high proportion of by-products was observed, thus making the reaction too inefficient to be profitable.

With the aim of suppressing side reactions responsible for the high proportion of by-products, the use of a more powerful electrophile was considered. Accordingly, attention was turned to the use of bromine, instead of iodine, in order to prepare bromotetrahydroquinoline (132).

Treatment of allylaniline (129) with one equivalent of bromine and sodium carbonate in dichloromethane in darkness at 0° for 30 min resulted in formation of a complex mixture of products, as evidenced by t.l.c. data and a ^1H n.m.r. spectrum with few clearly resolved signals. Whilst difficult to

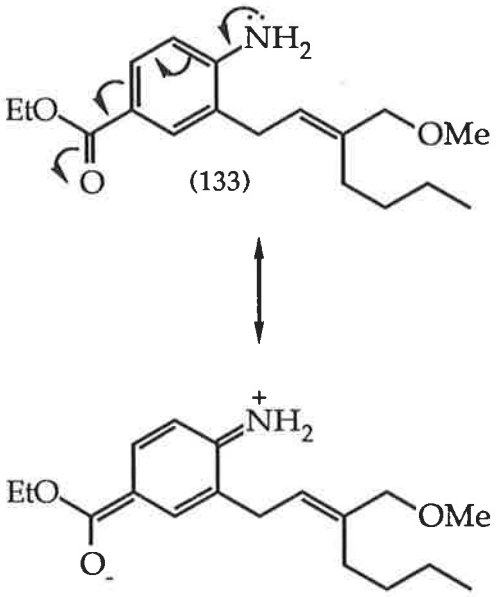
interpret because of its complexity, the ^{1}H n.m.r. spectrum did show resonances due to starting allylaniline (129) and a weak multiplet at δ 4.6. This resonance could be attributed to the hydrogen geminal to the bromine in (132), indicating a low yield of cyclized product. In addition, increased complexity in the region δ 6.35-7.4 may indicate bromination of the aromatic ring. The mass spectrum showed a peak at *m/z* 233 corresponding to the molecular ion for (129) and others at *m/z* 311 and 313 which could correspond to either (132) or a product resulting from monobromination of the aromatic ring.

The above results suggested that the free amine (129) may be too reactive and that alternative reaction pathways were being made more favourable than cyclization. It was therefore decided to evaluate use of the less nucleophilic trifluoroacetamide (126) in the iodine reaction.

Treatment of (126) with two equivalents of iodine and sodium carbonate in dichloromethane according to the standard procedure resulted in isolation of starting material only. A repeat reaction was carried out using saturated, aqueous, sodium carbonate solution in a two phase reaction instead of solid sodium carbonate in a heterogeneous reaction. This was done in an attempt to form an equilibrium concentration of amide anion to act as the nucleophile; however, starting material was again recovered after 46 h reaction time.

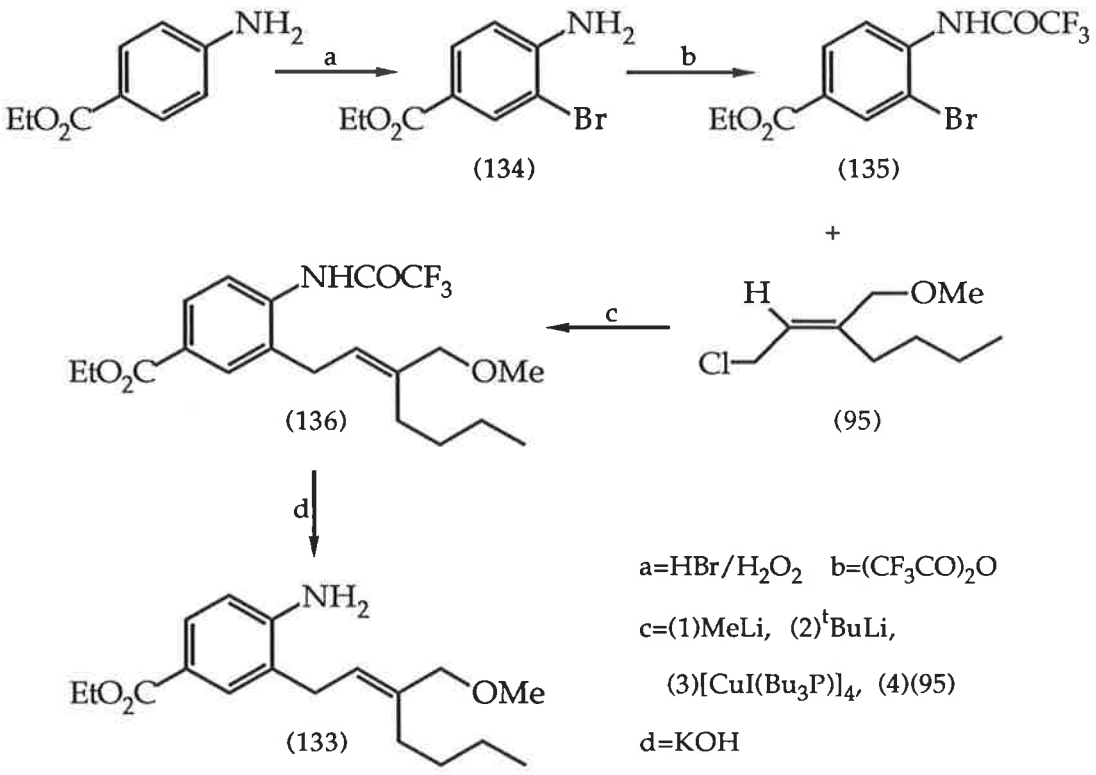
Since the iodine treatment resulted in decomposition of amine (129) and failed to cause a reaction with trifluoroacetamide (126), a compound of intermediate reactivity may suffice as substrate for this reaction. The ester (133) was thought to be a suitable candidate as it has a free amino group with

the nitrogen lone pair delocalized throughout the aromatic ring and ester function as shown below. This would lessen the nucleophilicity of the amino group.



The sequence of reactions chosen to prepare this compound was that shown in Scheme 42. It was recognized that the presence of the ester group may complicate the cuprate coupling reaction but since the reaction was to be carried out at low temperature, deprotonation and transmetallation may occur at a significantly faster rate than nucleophilic attack of the alkyllithium reagents on the carbonyl group which would enable satisfactory preparation of the desired cuprate species. The ester group of deprotonated (135) would also be less susceptible to nucleophilic attack than an isolated ester group due to delocalization of the negative charge of the amide anion. The fact that the carbonate group of allylic chloride (123) was found to be compatible with the

conditions employed in its coupling to the cuprate of (125) also lent support to the idea of attempting the coupling reaction shown in Scheme 42.



Scheme 42

Treatment of commercially available ethyl *para*-aminobenzoate with hydrobromic acid and hydrogen peroxide, according to a reported procedure[34], provided the bromo compound (134). Trifluoroacetylation afforded (135).

Attempted formation of the aryl cuprate species of (135) and subsequent reaction with (95) by the usual procedure resulted in the formation of an intractable mixture as indicated by t.l.c. and a poorly resolved ^{1}H n.m.r. spectrum. It was noticed in this reaction that during the course of the

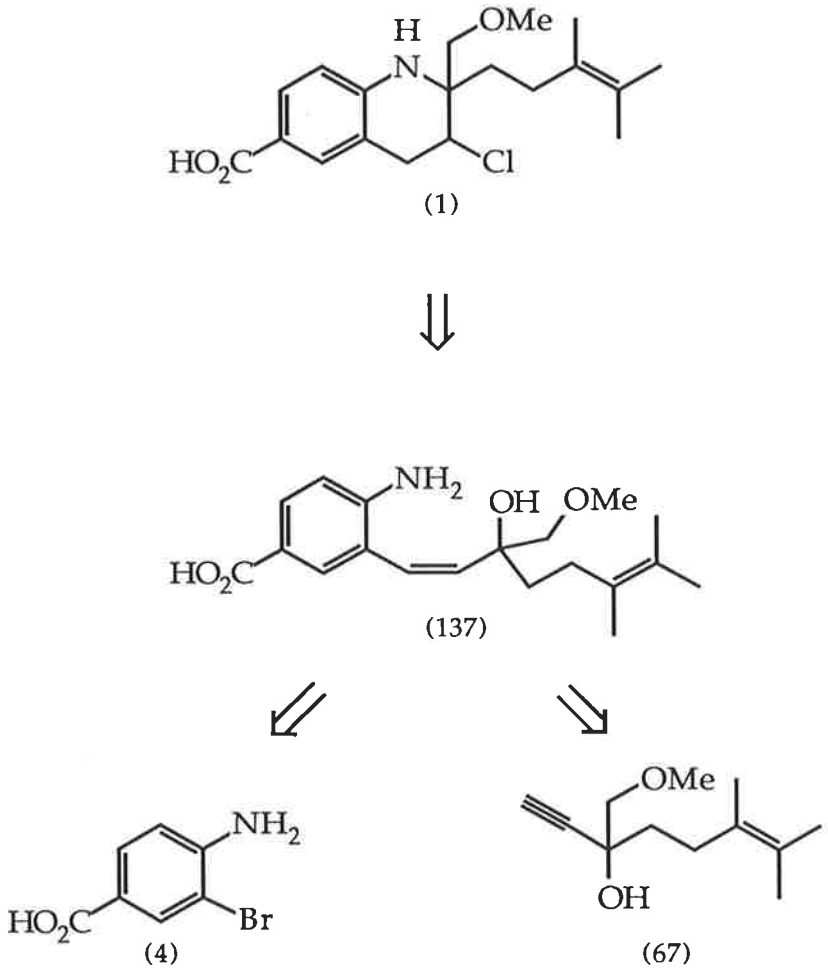
tert.-butyllithium addition to deprotonated (135) the solution turned an intense green colour which quickly changed to brown. This may have indicated transient formation of the desired dilithio species and subsequent decomposition. The dilithio species of the less conjugated compound (125) was an intense yellow colour. The ^{1}H n.m.r. spectrum of the product from this attempted coupling reaction with (135) showed no significant ethyl ester resonances, indicating that the ester group is incompatible with the conditions required for formation of the aryl cuprate species.

In summary, whilst the simple model compounds, dimethylallylanilines (19) and (30), underwent iodine initiated cyclization to produce iodotetrahydroquinolines (20) and (33), respectively[10], compounds (126) and (129) which have much larger allylic side chains, either failed to produce any cyclized product or only provided a very low yield of the desired iodotetrahydroquinoline. This may be due to the considerable steric bulk around the carbon atom bearing the butyl and methoxymethyl side chains. It follows that attack by the nitrogen atom on this carbon would be severely hindered, allowing other reaction pathways to become more favourable. With compounds (19) and (30), the steric factor is nowhere near as sizeable.

The results from this section of work led to the conclusion that electrophile initiated cyclization of allylanilines or derivatives with halogens is not an efficient method of constructing tetrahydroquinoline structures, except in cases where the allylic side chains are small. Since this is not the case with virantmycin or with the analogues we wished to prepare, attention was turned to another synthetic approach.

CHAPTER 3

An alternative retrosynthetic analysis suggested virantmycin (1) could be derived from submits (4) and (67) as shown in Scheme 43 below.

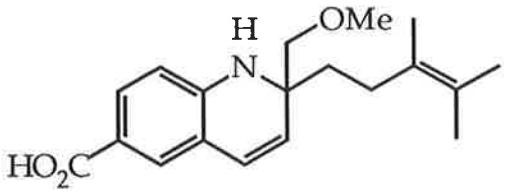


Scheme 43

The subunits (4) and (67) could be coupled in a palladium catalysed reaction as Hill and Raphael had done earlier[4,5]. Partial *cis*-hydrogenation of the resultant alkynylbenzene should afford the Z-hydroxyamine (137).

Cyclization of this compound under S_N1 conditions would provide heterocycle (138). An unfortunate consequence of this method of cyclization is that it is unlikely to allow stereochemical control.

The *N*-formyl, methyl ester derivative of (138) has been elaborated to racemic virantmycin by other workers[4,5].

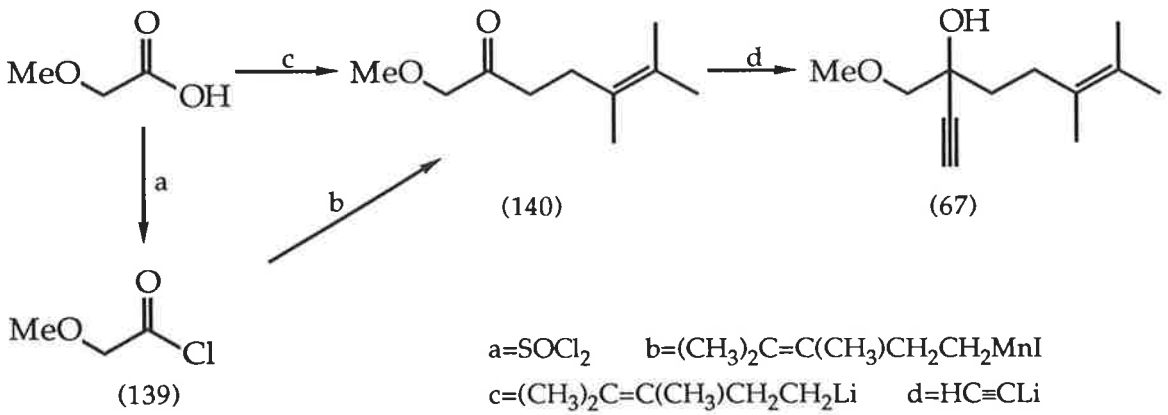


(138)

Hence, preparation of (138) and appropriate derivatization would constitute a formal synthesis of virantmycin.

It was noted earlier that Cooper[17] had coupled 3-chloro-3-methylbut-1-yne with ethyl *para*-aminobenzoate, using a copper catalyst, to afford the *N*-substituted compound (35) (Scheme 9). Presumably this reaction occurs via a propargylic cation intermediate under S_N1 conditions. The chloride was prepared from the corresponding alcohol using a copper catalyst in concentrated hydrochloric acid[17], again presumably via an S_N1 mechanism. We aimed to extend this approach to the intramolecular cyclization of systems such as (137). Ionization of the hydroxyl moiety would result in an allylic cation which could be trapped by the nearby amino group to form a heterocycle related to (138).

The proposed synthetic route to the subunit (67) began with methoxyacetic acid. Conversion of this acid to the acid chloride (139) and reaction with the organomanganous iodide derived from bromide (99) should afford the ketone (140). Alternatively, reaction of methoxyacetic acid with the alkyllithium reagent derived from (99) should give (140) directly. Treatment of (140) with lithium acetylide[4,5] would afford the subunit (67) (Scheme 44).



Scheme 44

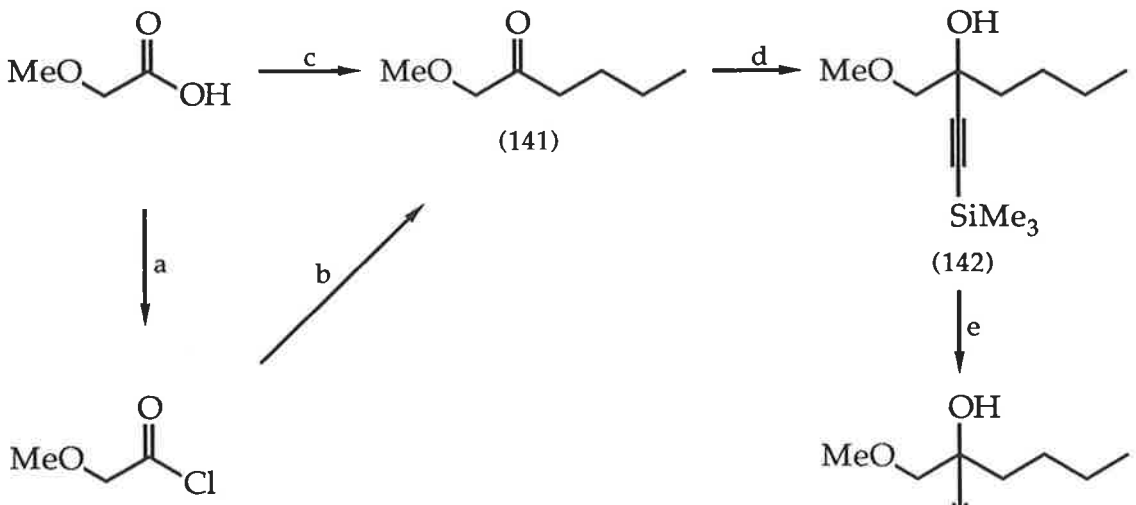
It has been reported that ketones can be prepared by the action of alkylmanganous halides on acyl halides[35]. Organomanganous reagents compare well to the large variety of organometallic reagents known for their ability to yield ketones from acid halides[35]. Manganese is cheap and the organomanganous reagents are easier to prepare than most others, such as the corresponding cadmium, zinc or copper species[35].

It has also been reported that ketones can be formed by the action of alkyllithium reagents on carboxylic acids directly, under carefully controlled conditions which minimize the amount of tertiary alcohol by-product[36].

The reaction of ketone (140) with lithium acetylide-ethylenediamine complex is known[4,5].

Methoxyacetyl chloride was prepared using a reported procedure[37], by refluxing methoxyacetic acid with thionyl chloride. An alternative method, using phosphorus pentachloride as reagent, provided a mixture of methoxyacetyl chloride and phosphorus oxychloride that could not be separated by fractional distillation.

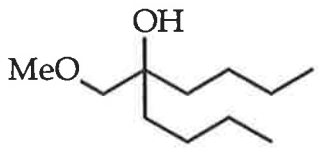
In order to make most efficient use of stocks of the valuable bromide (99), butyl bromide was used as a model to establish conditions for the reactions in Scheme 44 (Scheme 45).



(113) (143)

Scheme 45

Treatment of methoxyacetyl choride (139) with butylmanganous iodide, prepared from the corresponding Grignard reagent and manganous iodide in ether[35], afforded the ketone (141). The alternative, more direct method of treating methoxyacetic acid with 2.5 equivalents of butyllithium, under carefully controlled conditions[36], provided a product that comprised two major components, one of which was the desired ketone (141). The other component appeared to be the "overbutylated" alcohol (144) as the infrared spectrum showed a large hydroxyl absorption and the ^1H n.m.r. spectrum showed extra signals including singlets at δ 3.4 and 4.0 which could correspond to the methoxy and adjacent methylene hydrogens, butyl signals of higher integral than expected and a broad signal which disappeared on D_2O exchange.



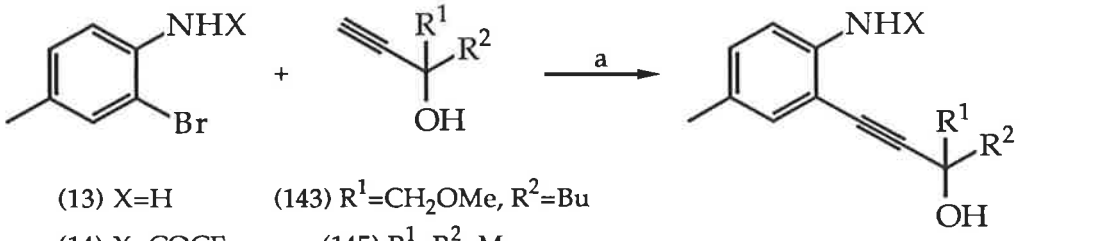
(144)

The organomanganous reagent enabled a more efficient conversion and hence was the method of choice for the synthesis of subunit (67).

Reaction of ketone (141) with lithium trimethylsilylacetylide in tetrahydrofuran at low temperature gave the carbinol (142). Subsequent treatment with tetrabutylammonium fluoride provided the terminal alkyne (143).

A more efficient method of preparing (143) from (141) involved treating the ketone with the Grignard reagent ethynylmagnesium chloride[38] in tetrahydrofuran.

The commercially available alkynol (145) was used in a model coupling reaction with aromatic subunit (14) (Scheme 46).



(13) X=H
(14) X=$COCF_3$

(143) R^1=CH_2OMe, R^2=Bu
(145) R^1=R^2=Me

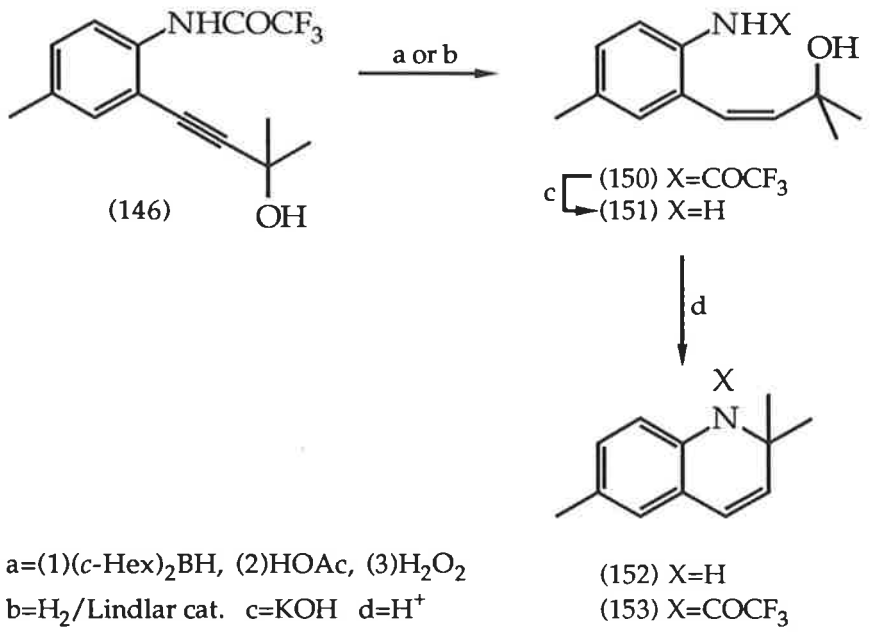
(146) X=$COCF_3$, R^1=R^2=Me
(147) X=$COCF_3$, R^1=CH_2OMe, R^2=Bu
(148) X=H, R^1=R^2=Me
(149) X=H, R^1=CH_2OMe, R^2=Bu

a=$PdCl_2(PPh_3)_2/PPh_3/CuI/Et_3N/py$

Scheme 46

Reaction of (14) and (145) in triethylamine/pyridine in the presence of a palladium(II)/copper(I) catalyst[39] gave the alkynylbenzene (146) in 65% yield. An analogous reaction using (143) provided (147) in 64% yield. This chemistry was found to be compatible with the free amino group of (13) and accordingly the aminoalcohols (148) and (149) were also prepared in satisfactory yield (Scheme 46).

The next step in the proposed strategy was partial hydrogenation of the triple bond to provide *cis*-alkenes for use in cyclization studies (Scheme 47).

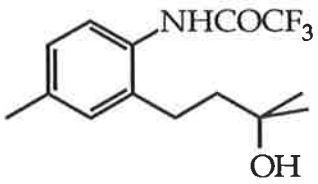


Scheme 47

An obvious first choice for reagent would be gaseous hydrogen in the presence of a Lindlar catalyst, but previous experience in our group indicated that Lindlar reductions were not always reproducible and were prone to overreduction.

It has been reported that alkynes can be stereospecifically reduced to *cis*-alkenes with dicyclohexylborane[40]. Treatment of (146) with 2.5 equivalents of dicyclohexylborane in tetrahydrofuran followed by oxidative workup according to the procedure of Millar and Underhill[40] resulted in recovery of starting material. Repetition of this reaction, except using 5 equivalents of the borane, provided the same result. Other workers have also been unable to reduce substituted propargylic alcohols with hindered boranes[41], so it was decided to return to the Lindlar reduction method.

Stirring (146) and Lindlar catalyst in ethyl acetate under a hydrogen atmosphere resulted in complete hydrogenation of the triple bond, producing alcohol (154).



(154)

Repetition, except stopping the reaction after approximately one molar equivalent of hydrogen had been consumed, provided a mixture of the desired product (150) and (154) in a *ca* 3:1 ratio.

It has been reported that in Lindlar semihydrogenation of 4-arylbut-2-yn-1-ols clean reduction to the Z-alkene was achieved when a small amount of quinoline and biphenyl was included in the reaction mixture[42]. This procedure was adapted for use in our system. Stirring (146), Lindlar catalyst and quinoline and biphenyl (20 and 10% of the mass of the alkyne substrate, respectively) in ethyl acetate under an atmosphere of hydrogen resulted in only one molar equivalent of hydrogen being consumed and production of the *cis*-alkene (150) in 90% yield. The ^{1}H n.m.r. spectrum of (150) showed a coupling constant between the vinyl protons of 12.3 Hz which is betwixt the usual ranges[63] for *cis*-alkenes (7-11 Hz) and *trans*-alkenes (12-18 Hz). It is well known that the Lindlar reduction of alkynes gives the *cis* isomer as the major product, but nevertheless the above data does not confirm *cis* geometry.

Attempts to grow crystals of (150) suitable for an X-ray crystallographic proof of structure were unsuccessful.

Hydrolysis of the trifluoroacetamide provided the free amine (151). The ^{1}H n.m.r. spectrum of aminoalkene (151) showed a coupling constant between the vinyl protons of 12 Hz, indicating that no isomerization had occurred in the hydrolysis reaction. Again, unfortunately, attempts at growing crystals suitable for X-ray analysis were unsuccessful.

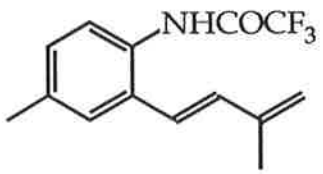
On the assumption of *cis*-geometry, alkenes (150) and (151) were employed in a cyclization study (Scheme 47).

It was envisaged that cyclization of (151) could be achieved under acidic conditions. This would enable the hydroxyl group to be ionized and although the amino group would be significantly protonated, there should be an equilibrium concentration of free amine present to trap the allylic cation and drive the equilibrium forward.

The conditions Cooper used to generate a cationic intermediate in the preparation of 3-chloro-3-methylbut-1-yne from the corresponding alcohol[17] were applied to (151). Stirring this compound with cuprous chloride, copper/bronze powder and calcium chloride in concentrated hydrochloric acid resulted in the formation of an intractable mixture as evidenced by a ^{1}H n.m.r. spectrum with no clearly resolved signals.

The trifluoroacetamide (150) was used in an analogous reaction and again an intractable mixture of products was obtained. Repetition with a shorter

reaction time, using a two phase system to lessen contact between the substrate and concentrated acid and including a base wash in the workup, in order to minimize decomposition, also resulted in a complex mixture. Flash chromatography of the mixture enabled isolation of a major product which appeared to be the diene (155) resulting from dehydration of (150).



(155)

The product had an ultraviolet absorption maximum at 280 nm, compared to 207 nm in (150), indicating increased conjugation and there was no hydroxyl absorption in the infrared spectrum. The ^{1}H n.m.r. spectrum showed the disappearance of one aliphatic methyl resonance and a downfield shift of the other into the allylic methyl region at δ 1.96, appearance of a broad singlet at δ 5.17 attributable to the terminal vinyl protons and a coupling constant of 16.0 Hz between the non-terminal vinylic protons indicating a *trans* relationship. The mass spectrum showed a strong molecular ion at *m/z* 269 which is expected for (155).

An alternative and perhaps less harsh set of conditions which could induce S_N1 type cyclization would be small amounts of an acid in an organic solvent. A recent report showed that methanesulphonic acid in dichloromethane can be a suitable medium in which to form carbocations[43] so this reagent was employed for use in our system. When the amide (150) was stirred in

dichloromethane in the presence of approximately 6 equivalents of methanesulphonic acid at room temperature for 1 h, an intractable mixture of products was obtained, as indicated by t.l.c. and a very poorly resolved ^{1}H n.m.r. spectrum. An analogous reaction using benzene as solvent provided the same outcome. A further reaction in dichloromethane at −10° for 20 min also resulted in an intractable mixture.

The use of acetic acid as an ionizing medium in which to achieve cyclization was investigated. The amine (151) was stirred in refluxing acetic acid. Analysis of the reaction progress by t.l.c. appeared to indicate slow consumption of starting material, hence a long reaction time was allowed. After 24 h, t.l.c. appeared to show that some starting material remained, however after workup, analysis of the product by ^{1}H n.m.r. spectroscopy revealed that a complex mixture of products was again obtained.

The complexity of product mixtures obtained in the above series of reactions seemed to suggest that the chosen reaction conditions were too harsh. Consequently, a milder method of cyclization was sought.

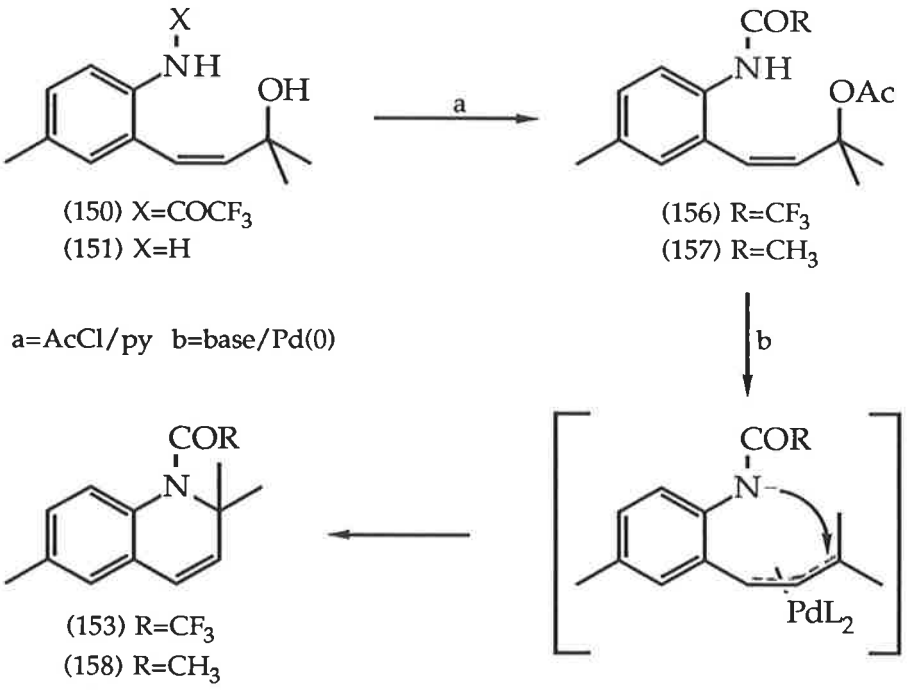
The use of hexafluoroisopropanol as both reagent and solvent was investigated. It was envisaged that the high polarity of this solvent may induce ionization of the tertiary hydroxyl group and that decomposition may be minimized due to the absence of a strong acid. The amine (151) was treated with refluxing hexafluoroisopropanol for 21 h, at which stage t.l.c. analysis indicated that negligible reaction had occurred, so a catalytic amount of *para*-toluenesulphonic acid was added and the mixture refluxed for a further 4 h. The product obtained after workup was yet again a complex mixture and

subsequent flash chromatography was unsuccessful in isolating any purified materials.

The lack of success after employing the wide variety of conditions described above led to abandonment of the acid-catalysed cyclization method. Another mode of cyclization was sought.

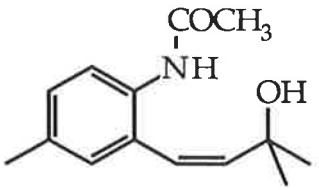
It has been reported that allylic alcohols, as well as esters and ethers, will react rapidly with primary or secondary amines to give allylic amines in high yield using a palladium-triphenylphosphine complex catalyst[44]. An intramolecular version of this reaction would enable the desired cyclization of (151) so the method was adapted for application to our case. The aminoalcohol (151) was treated with catalytic quantities of palladium acetate and triphenylphosphine in refluxing acetonitrile. Analysis of the crude product by t.l.c. indicated a complex mixture of products. Flash chromatography did provide a major fraction but the ^{1}H n.m.r. spectrum of this material had no clearly resolved signals and the infrared spectrum was complex, as was the mass spectrum. There was no clear indication of the presence of the desired heterocycle (152).

It was thought that the palladium catalysed reaction would be facilitated if the hydroxyl group was converted to a better leaving group. Allylic acetates are known to undergo palladium catalysed coupling with nitrogen nucleophiles[44,45] so conversion of (150) and (151) to the corresponding mono- and diacetylated compounds (156) and (157) respectively, was investigated. It was planned to use the amide anion as the nucleophile in the palladium catalysed reaction (Scheme 48).

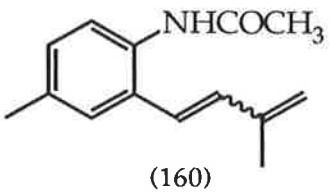


Scheme 48

Treatment of (151) with excess of acetyl chloride in pyridine at room temperture overnight followed by dilute acid workup resulted in an intractable product mixture. Repetition, but at 0° for 90 min and without the acid workup, resulted in a product that was separated into two main fractions by flash chromatography. On the basis of their spectral data, these fractions appeared to be the amide (159) and the diene (160) which presumably formed via elimination of acetic acid from the desired product (157).



(159)



(160)

The infrared spectrum of the higher R_F fraction contained no hydroxyl absorption and showed a strong amide carbonyl absorption at 1682 cm^{-1}. The ^1H n.m.r. spectrum showed an allylic methyl resonance at δ 1.95, an acetyl methyl resonance at δ 2.2 and a terminal vinyl proton resonance at δ 5.1. The non-terminal vinyl proton resonances were overlaid with a broad impurtiy resonance, preventing determination of double bond geometry. The mass spectrum showed a molecular ion at *m/z* 215. This data is consistent with the structure (160). The infrared spectrum of the lower R_F fraction contained a hydroxyl absorption as well as a strong amide carbonyl absorption. The ^1H n.m.r. spectrum showed an acetyl methyl resonance at δ 2.15 and a doublet due to the aromatic proton *ortho* to the nitrogen atom at δ 7.75. This significant downfield shift relative to the corresponding signal at δ 6.45 in the spectrum of the starting material is common in many *N*-acylated anilines[10]. It is due to the carbonyl oxygen atom lying in close proximity to the *ortho* proton which therefore experiences a strong anisotropic effect[10]. The mass spectrum showed a molecular ion at *m/z* 233. The spectral data for this fraction is consistent with structure (159).

The trifluoroacetamide (150) was treated with acetyl chloride in pyridine at room temperature and the reaction progress followed by t.l.c. This analysis revealed a slow conversion of starting material to several products. The ^1H n.m.r. spectrum of the crude product contained no clearly resolved signals which suggested a complex mixture of components.

The above results suggested that acetylation of allylic, tertiary alcohols (150) and (151) was not straightforward and that concomitant or subsequent

reactions such as elimination were occurring. The acetylation reactions were not efficient enough to warrant further investigation.

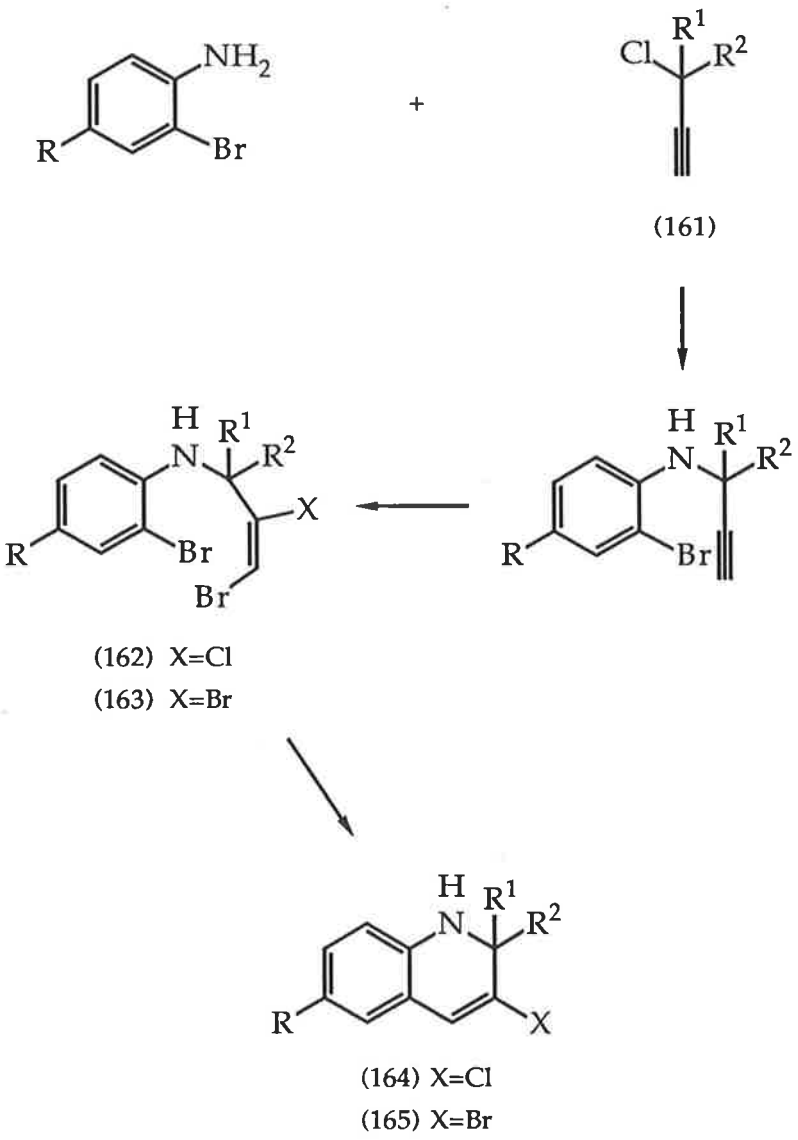
In summary, ring closure of amidoalcohol (150) and aminoalcohol (151) could not be achieved using a wide variety of conditions.

In most of the attempted ionization, and later, acetylation, reactions involving the allylic, tertiary hydroxyl group of (150) and (151), a complex mixture of products was obtained. This suggests that the allyl alcohol portion of the molecules was too reactive under the conditions and that cyclization was one of the less favourable reaction pathways. In any case the approach was proved not to be profitable and, accordingly, attention was then directed at designing an alternative synthetic approach.

It was interesting to note that during the concluding stages of this section of work, Hill and Raphael published a full account[5] of their 1986 synthesis of racemic virantmycin which included the comment "We had hoped to produce the heterocycle by partial, catalytic hydrogenation of the triple bond and subsequent cyclization of the resulting Z-hydroxyamine. However, all attempts to achieve this were fruitless". This comment did not appear in the initial communication[4]. Our work only serves to confirm this statement.

CHAPTER 4

Another synthetic approach to virantmycin-like systems reverses the order of formation of the two key bonds relative to the approach described in Chapter 3. The key steps are shown in Scheme 49 below.



Scheme 49

Suitably substituted chloro subunits (161) could be prepared from the corresponding alcohols by adapting the method of Cooper[19]. Alcohols of the required type were prepared earlier (see Chapter 3, Scheme 45).

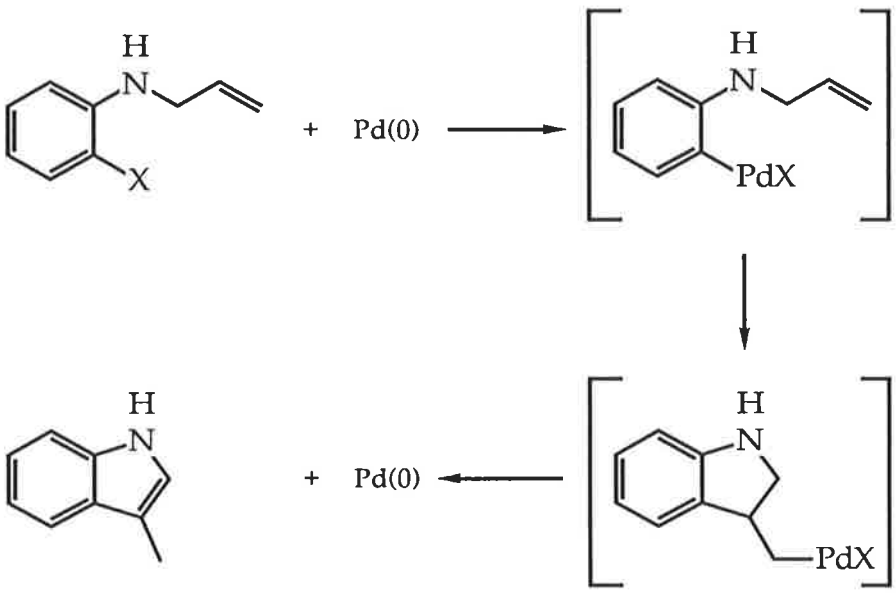
Copper-catalysed coupling of chlorides (161) with the amino moiety of *ortho*-bromoanilines should afford substituted *N*-propargylanilines. For reasons explained in Chapter 3, this reaction is unlikely to allow stereochemical control. Treatment of the *N*-propargylated compounds with a modified form[46] of the commercially available anion-exchange resin Amberlyst A-26 could provide *E*-chlorobromo compounds (162). Alternatively, bromination of the *N*-propargylanilines with molecular bromine in chloroform[47,48] should afford *E*-dibromoalkenes (163), provided no ring bromination occurred. Other members of the Adelaide group[48] have shown that the coupling reaction occurs only with acetylenic chlorides. Corresponding dibromoalkenyl chlorides did not couple with anilines[48].

A palladium catalysed cyclization of the vinylstannane[49,50] derived from (162) or (163) *in situ* could provide C-3 halofunctionalized dihydroquinolines (164) and (165).

It is known that double bond geometry is retained in palladium catalysed coupling reactions[41,49,51-54], hence the particular stereoisomers of precursors (162) and (163) shown in Scheme 49 are required for closure to the heterocycles (164) and (165).

A related method that might be considered for cyclization of these systems is the "Heck" arylation of 2-halo-*N*-allylanilines[55]. This method results in

formation of the five-membered heterocyclic ring with the simple allyl system[55] (Scheme 50).

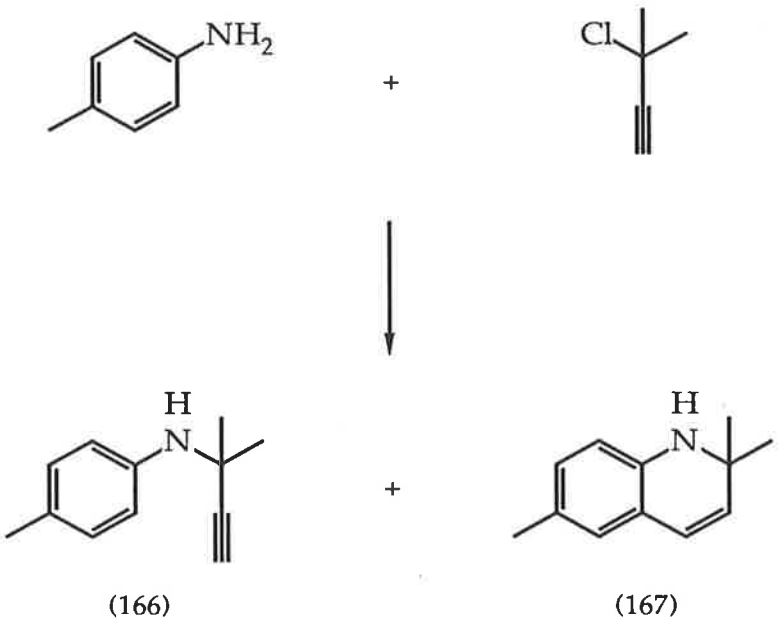


Scheme 50

However, in our case, the allylic carbon atom bears no hydrogens and this would prevent anomatization which is a likely driving force for closure to the five-membered ring system shown. Hence, the "Heck" reaction of disubstituted allyl systems could quite possibly result in cyclization to give the six membered ring product (Scheme 51).

Scheme 51

Easton and Cassady[56] have reported that 2,2,6-trimethyl-1,2-dihydroquinoline (167) is formed as a by-product in the copper-catalysed coupling of *p*-toluidine with 3-chloro-3-methylbut-1-yne (Scheme 52).

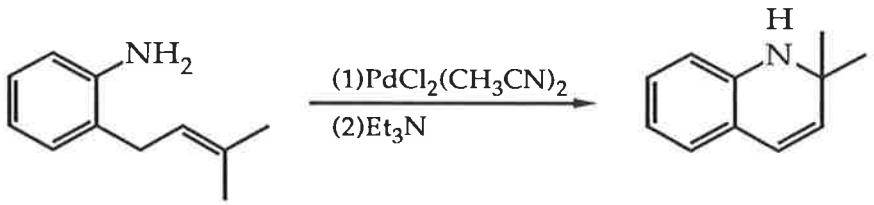


(166) (167)

Scheme 52

Further, the desired product, *N*-propargylaniline (166) was slowly converted to dihydroquinoline (167) under the original alkylation conditions[56]. This procedure was later employed to prepare a variety of 2,2-dimethyl-1,2-dihydroquinolines[57].

Hegedus and co-workers[58,59] have reported a preparation of 2,2-dimethyl-1,2-dihydroquinoline, involving palladium catalysed cyclization of the allylaniline (30) (Scheme 53).

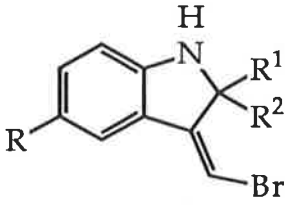


(30)

Scheme 53

Dihydroquinolines prepared by the "Heck", "Easton" or "Hegedus" reactions outlined above would be unsubstituted at C-3. In terms of a virantmycin or analogue synthesis, the problem of elaboration to a C-3 halofunctionalized tetrahydroquinoline structure would remain. Since this problem has already been faced and overcome at Cambridge[4,5] (this was briefly discussed in the Introduction), it was of interest in the current study to investigate palladium catalysed cyclization of vinylstannanes derived from the dihalofunctionalized *N*-allylanilines (161) and (162) *in situ* as the desired products would contain an in-built halogen substituent at C-3. This should enable a shorter elaboration to virantmycin-like structures.

It was envisaged that use of the terminally bromofunctionalized *N*-allylanilines (162) and (163) in the cyclization reaction should facilitate formation of a six-membered ring due to ease of palladium insertion into the terminal carbon-bromine bond[60]. However, the presence of a vinylic halogen atom at the other end of the double bond may allow competitive formation of the corresponding five-membered heterocycle (168) in the palladium reaction.



(168)

It was of interest to determine whether five or six-membered heterocyclic ring formation was favoured in the palladium catalysed cyclizations of (161) and (162). There are two bulky groups attached to the carbon adjacent to the internal alkene carbon and this would be expected to sterically hinder cyclization to a five-membered ring in both cases. In the case of compound (161) the rate of palladium insertion into the carbon-chlorine bond relative to that into the carbon-bromine bond may also determine which ring size is favoured. It has been reported that in palladium catalysed coupling of organic halides, the order of reactivity Br>>Cl is usually observed[49]. It therefore seems reasonable, after considering the steric factors noted above, to predict preferential six-membered heterocycle formation.

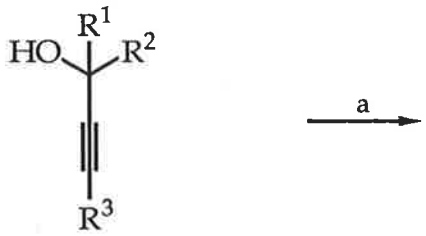
The successful preparation of the six-membered heterocycles (164) and (165) would establish methodology for extension to synthesis of 3-halo-1,2-dihydroquinoline analogues of virantmycin.

It would be of interest to determine the biological activity of these compounds. They contain a vinylic halide moiety and are therefore unable to undergo intramolecular halogen displacement to form aziridines. It is possible that an aziridine is a key intermediate in the mechanism of virantmycin's biological action. Hence, determining the activity of 3-halo-1,2-dihydroquinoline analogues may shed some light on the mode of action of virantmycin.

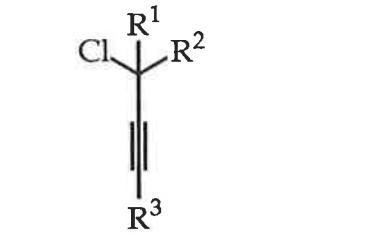
It was also of interest to prepare 3-halotetrahydroquinolines from the corresponding dihydroquinolines Since hydrogenation of (164) and (165) with the restriction of leaving the C-3 halogen substituent intact may be difficult, the following, alternative procedure could be used. Hydrolysis of the

vinyl halides with mercuric trifluoroacetate in either trifluoroacetic acid or acetic acid containing boron trifluoride etherate[61] should give the corresponding ketone. Subsequent borohydride reduction to the alcohol and chlorination of the C-3 hydroxyl group[4,5,6] should provide the desired structures.

The viability of the initial coupling and cyclization steps was evaluated. The tertiary, propargylic alcohols (145) and (142) (which was prepared earlier-see Chapter 3, Scheme 45), were converted to the corresponding chlorides and subsequently coupled to anilines (Scheme 54).

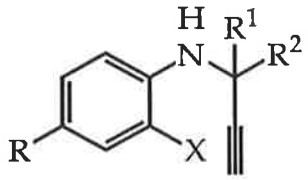


(145) R^1=R^2=Me, R^3=H
(142) R^1=CH_2OMe, R^2=Bu, R^3=$SiMe_3$

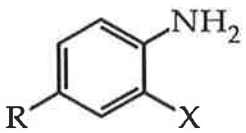


(169) R^1=R^2=Me, R^3=H
(170) R^1=CH_2OMe, R^2=Bu, R^3=$SiMe_3$
(171) R^1=CH_2OMe, R^2=Bu, R^3=H

+



(172) R=X=H, R^1=R^2=Me
(173) R=X=H, R^1=CH_2OMe, R^2=Bu
(174) R=Me, X=Br, R^1=R^2=Me
(175) R=Me, X=Br, R^1=CH_2OMe, R^2=Bu
(176) R=CO_2Et, X=Br, R^1=R^2=Me



(13) R=Me, X=Br
(134) R=CO_2Et, X=Br

a=$HCl/CaCl_2/CuCl/Cu$ b=$CuCl/Cu/Et_3N$

Scheme 54

As a trial, the alcohol (145) was converted to the corresponding chloride (169) and the chloride coupled with aniline by the method of Cooper[19] to give the *N*-propargylaniline (172).

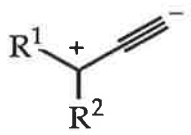
The chloride (170) is a closer model than (169) since it contains much larger groups attached to the tertiary, propargylic carbon atom that is attacked by the amino group in the coupling reaction. Conversion of alcohol (142) to the chloride (170) was achieved by modifying the method of Cooper[19]. The copper-catalysed coupling of chloride (170) with aniline did not occur after 34 h at reflux in Cooper's two phase ether/water system[19] but did proceed at a satisfactory rate in a refluxing tetrahydrofuran/water mixture to provide amine (173) in 52% yield. This compound was obtained in similar yield from a tetrahydrofuran/water reaction at room temperature but the conversion required 4 days.

Coupling of 2-bromotoluidine (13) with chlorides (145)[48] and (170) in refluxing tetrahydrofuran/water afforded the *N*-substituted anilines (174)[48] and (175), respectively.

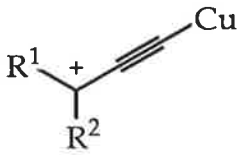
It was necessary for the copper-catalysed coupling reaction to be tolerant of the methoxymethyl group in order for the conversion to be part of a synthesis of virantmycin and close analogues. The successful preparation of compounds (173) and (175) confirms this.

The yields of (173) and (175) were only moderate and it was interesting to note that the trimethylsilyl moiety attached to the triple bond of chloride (170) was removed under the reaction conditions. This unexpected result was useful in

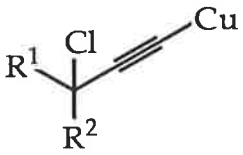
the sense that desilylation was intended to be the following step. The slower rate and lower yield than expected in these reactions may be rationalized by considering the mechanism. It has been suggested that the coupling reaction proceeds through a dipolar intermediate (177)[62].



(177)



(178)



(179)

While the mechanistic role of cuprous salts is not known[62], it may be that the dipolar intermediate (177) is made more reactive in the form of the acetylide structure (178)[62]. Alternatively, the tertiary acetylenic chloride used may form its acetylide (179) in the basic reaction mixture, subsequently leading to (178) and/or (177) as the species responsible for the alkylation[62].

The chloride (170) does not have a terminal acetylene group with which to form intrmediates (177), (178) or (179) directly. The slower than expected reaction rate may be due to the extra desilylation step that would be required to form the dipolar intermediate (177). The desilylation step may have a relatively high activation energy which would decrease the reaction rate and possibly allow other reaction pathways to become more favourable, lowering the yield of coupled amine. The observation that the crude products from these reactions were dark coloured mixtures and the fact that careful chromatography was required to isolate the desired products supports the above suggestion.

Consequently, coupling of anilines with the desilylated chloride (171), which contains a terminal triple bond, should proceed at a faster rate and in higher yield than the silylated compound (170).

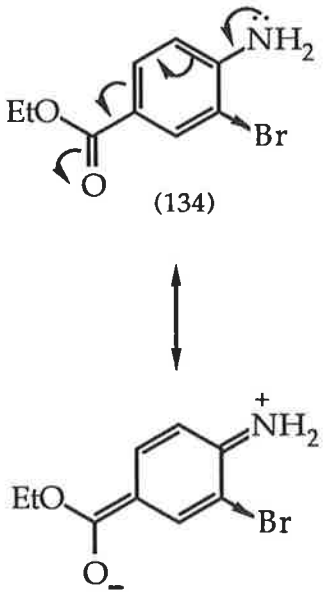
The use of aminoester (134) in this type of reaction was investigated. Successful coupling of the compound would eliminate the need for elaboration of the *para* methyl group to a carboxyl function at a later stage, although this elaboration should be possible using Raner's procedure[10], outlined in Scheme 3 followed by oxidation of the benzylic alcohol moiety.

Reaction of aminoester (134) with acetylenic chloride (169) using similar conditions to those of Cooper[19] returned, after chromatography, mainly the starting material (134) along with a very low yield of a compound whose spectral data was consistent with the sturcture of the desired coupling product (176).

The infrared spectrum of this product showed only one NH absorption at 3408 cm^{-1}, which is typical for a secondary amine[63], compared to two NH_2 absorptions in the spectrum of the starting, primary amine (134). The infrared spectrum of the product also showed an absorption at 3304 cm^{-1} which is attributable to a terminal, acetylenic proton. The ^1H n.m.r. spectrum showed a broad signal at δ 4.7 integrating for one proton which disappeared on D_2O exchange, an aliphatic dimethyl resonance at δ 1.7 and a singlet resonance at δ 2.3, attributable to a terminal acetylenic hydrogen. The mass spectrum showed a molecular ion at *m/z* 309/311, which is expected for the desired *N*-substituted amine (176).

An analogous reaction was carried out at reflux, except using tetrahydrofuran instead of ether, in order to allow a higher temperature. This modification did not increase the yield. Hence the reaction was not considered efficient enough to be synthetically useful.

The low yield can be attributed to the decreased nucleophilicity of the amino group due to delocalization of the nitrogen lone electron pair throughout the aromatic ring and ester function and the inductive electron withdrawing effect of the bromo substituent.



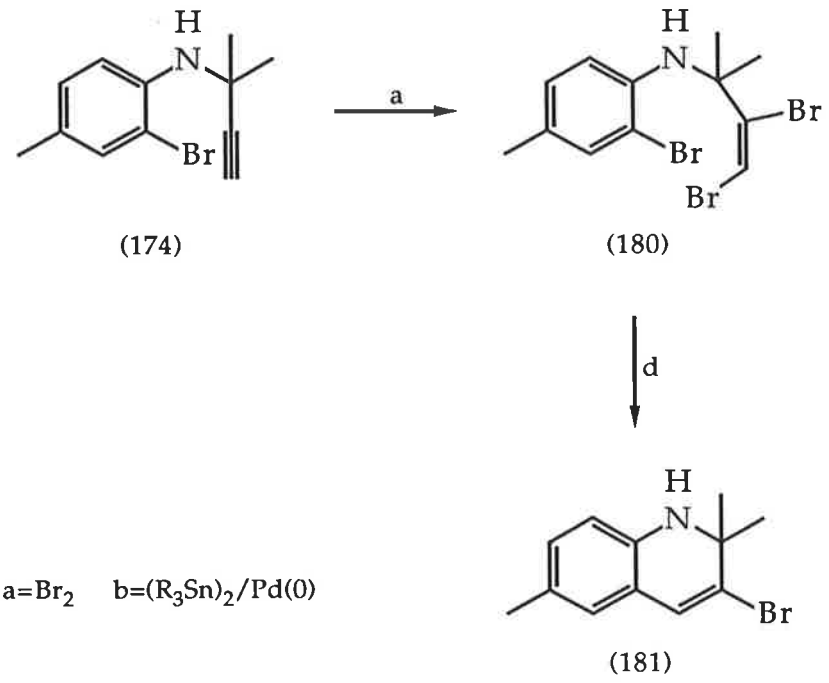
(134)

It was therefore concluded that introduction of the ester group should be delayed until after the coupling reaction.

The successful synthesis of *N*-propargylanilines (174) and (175) enabled a cyclization study to be undertaken. Before exploring the chemistry outlined

in Scheme 41, the possible radical cyclization of the *N*-propargylaniline (175) with tributylstannane was briefly investigated. Reaction of this compound with tributylstannane, with regular additions of a catalytic quantity of azobisisobutyronitrile every 20 h, in refluxing benzene for 95 h resulted in recovery of the starting material (175).

It is known that bromination of acetylenes with molecular bromine in chloroform provides predominantly the *E*-dibromoalkene[47,48]. Of the methods for functionalization of triple bonds outlined in Scheme 49, bromination with molecular bromine in chloroform would represent the shortest and easiest route to precursors for palladium catalysed cyclization. Hence this was the first method investigated, using the readily accessible model compoud (174) (Scheme 55).



(174) (180) (181)

Scheme 55

Bromination of alkyne (174) to provide dibromoalkene (180) was accomplished by the procedure of March[48], using 2.5 equivalents of bromine in chloroform at 0°. The diagnostic feature of the ^{1}H n.m.r. spectrum of compound (180) was the vinyl proton resonance at δ 6.95, its appearance downfield due to the two vinylic bromine atoms. The corresponding proton in the starting material (174), i.e. the terminal, acetylenic hydrogen, resonated at δ 2.23.

Treatment of (180) with hexabutyldistannane, *tetrakis*(triphenylphosphine)palladium(0) and a trace of 2,6-di*tert*-butyl-4-methylphenol in refluxing 1,4-dioxane for 25 h resulted in a crude product mixture consisting mostly of tribulylstannanes and the starting material, according to t.l.c. and ^{1}H n.m.r. data.

It is possible that the large steric bulk of both hexabutyldistannane and the palladium complex would hinder palladium initiated cleavage of the tin-tin bond, resulting in retardation of vinylstannane formation.

It was thought that this problem may be alleviated by employing a less bulky stannane reagent and, accordingly, hexamethyldistannane was used in an analogous reaction. Treatment of tribromide (180) with hexamethyldistannane, *tetrakis*(triphenylphosphine)palladium(0) and a trace of 2,6-di*tert*-butyl-4-methylphenol in refluxing 1,4-dioxane for 20 h afforded a mixture of products. Three main fractions were isolated from the crude product mixture by flash chromatography. One fraction contained the starting material (180) and another contained, surprisingly, the *N*-propargylaniline (174). The presence of this compound may have been due

to incomplete bromination in the previous step, however, this was considered to be unlikely as compound (174) was not detected by t.l.c. or ^{1}H n.m.r. spectroscopic analysis of the dibromoalkene. Alternatively, production of the alkyne may have resulted from debromination of (180) in the palladium/stannane reaction. This could suggest that vinylstannane formation did occur and that an elimination pathway is competitive with cyclization. The third fraction contained, again surprisingly, the aniline (13), presumably resulting from dealkylation of (180). The dealkylation may be facilitated by action of tin as a Lewis acid, co-ordinating to the nitrogen atom. This complexation, combined with the inductive, electron withdrawing effect of the two bromo substituents, may weaken the nitrogen to tertiary carbon bond enough to cause its cleavage.

The above results implied that considerably more work needs to be done on the palladium/stannane reaction in order to make cyclization a more, and preferably the most, favourable pathway. Unfortunately, time restraints prevented any further investigation of this synthetic approach from being part of the current study.

EXPERIMENTAL

GENERAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Microanalyses were performed by the Canadian Microanalytical Service, Vancouver. Ether refers to diethyl ether. Light petroleum refers to a fraction of boiling range 66-68°. Analytical thin layer chromatography (t.l.c.) was performed using Merck Kieselgel $60F_{254}$ silica on aluminium backing plates. Flash chromatography[64] refers to nitrogen-pressure driven rapid chromatography using Amicon Matrex Silica, pore diameter 60Å. Squat chromatography refers to "dry column" flash chromatography[65] using Merck Kieselgel HF_{254} silica. Drying and other purification of organic solvents was accomplished by standard laboratory procedures[66,67]. All organic extracts were dried over anhydrous magnesium sulphate unless otherwise stated.

Ultraviolet spectra were recorded on a Pye Unicam SP 8-100 spectrophotometer. Infrared spectra were recorded on a Jasco IRA-1 grating spectrometer or a Hitachi 270-30 spectrometer. Proton nuclear magnetic resonance (^{1}H n.m.r.) spectra were recorded on a Varian T60 or Jeol JNM-PMX 60 spectrometer operating at 60 MHz in carbon tetrachloride solution unless otherwise specified. ^{13}C and some ^{1}H n.m.r. spectra were recorded using a Bruker WP80DS spectrometer operating at 20.1 or 80 MHz respectively or a Bruker CXP300 or a Bruker ACP300 spectrometer operating at 75.47 or 300 MHz. Tetramethylsilane was 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). Multiplicities are abbreviated to:- s, singlet, d,

doublet, t, triplet, q, quartet, m, multiplet, br, broad. Mass spectra were recorded on an AEI MS3074 spectrometer operating at 70 eV. Fast Atom Bombardment (F.A.B.) mass spectra and Mass-Analyzed Ion Kinetic Energy Spectra (MIKES) were recorded on a VG ZAB 2HF spectrometer. Only the major fragments are given with their relative abundances shown in parentheses.

CHAPTER 1

4-Dimethylamino-2-butyn-1-ol (8)

Prepared by the procedure of Salvador and Simon[15], b.p. 67-69°/0.5 mm (lit.[15] 76-78°/1.5 mm). ^{1}H n.m.r. δ ($CDCl_3$) 2.35, s, $N(CH_3)_2$; 3.3, t, *J* 2 Hz, CH_2N; 4.3, t, *J* 2 Hz, CH_2O; 4.65 (varies with sample concentration), s, OH. Mass spectrum *m/z* 113 (M, 7%), 112 (6), 96 (1), 94 (2), 82 (6), 58 (5), 44 (11), 42 (11), 40 (32), 32 (84), 28 (100).

(E)-2-(2-N,N-*Dimethylaminoethylidene)hexan-1-ol (93)*

The aminobutynol (8) (6 g, 53 mmol) in anhydrous ether (60 ml) was slowly added to a stirred solution of butylmagnesium bromide (210 mmol) in anhydrous ether (200 ml) under an atmosphere of nitrogen. The resulting mixture was stirred under nitrogen at room temperature for 10 h and then quenched by the addition of saturated, aqueous ammonium chloride solution. The aqueous layer was extracted with ether and the combined ether layers were washed with brine, dried and evaporated to give the *alcohol* (93), (8.15 g, 90%) as a yellow oil, b.p. 61-63°/0.04 mm (Found: C, 69.6; H, 12.2. $C_{10}H_{21}NO$ requires C, 70.1; H, 12.4%). ν_{max} (film) 3200-3400 (OH), 1670 cm^{-1} (w) (C=C). ^{1}H n.m.r. δ ($CDCl_3$) 0.7-1.6, br, $CH_3CH_2CH_2$; 2.1, m, C=C-CH_2; 2.25, s, $N(CH_3)_2$; 3.0, d, *J* 7 Hz, CH_2N; 4.1, s, CH_2O; 4.2 (varies with sample

concentration), s, OH; 5.6, t, *J* 7 Hz, C=C-H. Mass spectrum *m/z* 171 (M, 15%), 154 (8), 140 (11), 128 (5), 58 (86), 45 (100).

Attempted O-methylation of the aminoalcohol (93) (sodium hydride/ether/dimethylformamide)

The aminoalcohol (93) (1 g, 5.84 mmol) in anhydrous ether (4 ml) was added to a stirred suspension of sodium hydride (0.212 g, 8.76 mmol) in anhydrous ether (10 ml) under an atmosphere of nitrogen. After stirring for 10 min, freshly distilled, anhydrous iodomethane (0.4 ml, 0.912 g, 6.44 mmol) was added, followed by anhydrous dimethylformamide (5 ml). The resultant, heterogeneous mixture was stirred at room temperature for 1 h and then heated under reflux for 3 h. The mixture was quenched by the careful addition of water, then acidified with concentrated hydrochloric acid. The aqueous layer was extracted thrice with ether , made basic by the addition of aqueous potassium hydroxide solution (30%) and extracted thrice again with ether. The combined base extracts were dried and evaporated to give a yellow oil (0.68 g) which corresponded by t.l.c., ^{1}H n.m.r. spectroscopy and mass spectrometry to unreacted (93) containing a small amount of the desired product (94) since additional singlets appeared at δ 3.3 and δ 3.85 in the ^{1}H n.m.r. spectrum and an additional peak appeared at *m/z* 185 in the mass spectrum.

(E)-N-*(3-Methoxymethyl-2-hepten-1-yl)*-N,N,N-*trimethylammonium iodide (96)*

The aminoalcohol (93) (0.20 g, 1.17 mmol) in anhydrous tetrahydrofuran (3 ml) was slowly added to a stirred suspension of sodium hydride (80% dispersion in paraffin oil, 0.06 g, 2 mmol) in anhydrous tetrahydrofuran (5 ml) under an atmosphere of nitrogen. The resulting mixture was stirred under nitrogen at room temperature for 15 min. Iodomethane (0.25 ml, 0.57 g, 4 mmol) was added dropwise and the mixture stirred under nitrogen at room temperature for 24 h. Saturated, aqueous, ammonium chloride solution was added, followed by dichloromethane. The aqueous layer was extracted twice with dichloromethane. The combined organic layers were dried and evaporated to yield the *salt* (96) (0.27 g, 71%) as a yellow solid which was recrystallized from acetone/hexane to give colourless crystals, m.p. 122-122.5° (Found: C, 43.7; H, 7.9. $C_{12}H_{26}INO$ requires C, 44.0; H, 8.0%). ^1H n.m.r. δ ($CDCl_3$) 0.7-1.6, br, $CH_3CH_2CH_2$; 2.3, m, C=C-CH_2; 3.4, s, CH_3O; 3.5, s, $^+N(CH_3)_3$; 4.0, s, CH_2O; 4.35, d, *J* 8 Hz, CH_2N^+; 5.75, t, *J* 8 Hz, C=C-H. F.A.B. mass spectrum (glycerol matrix) *m/z* 200 ($C_{12}H_{26}NO^+$, 100%), 141 (9), 109 (4).

The reaction was also carried out using dimethyl sulphoxide as solvent in an analogous procedure (except the reaction time was reduced to 2 h) which provided (96) in 57% yield.

Attempted preparation of (E)-*1-Bromo-3-methoxymethylhept-2-ene (97)*

A saturated solution of lithium bromide in acetone (10 ml) was added to a solution of the quaternary ammonium salt (96) (0.068 g) in acetone (0.5 ml) under an atmosphere of nitrogen. The resultant mixture was stirred under nitrogen at room temperature overnight and then heated under reflux for 2 d. The mixture was evaporated and the residue partitioned between water and dichloromethane. The organic layer was dried and evaporated to give a solid which corresponded by t.l.c. and ^{1}H n.m.r. spectroscopy to unreacted (96).

Attempted O-*methylation of the aminoalcohol (93) (diazomethane/boron trifluoride etherate)*

Boron trifluoride etherate (0.30 ml, 0.35 g, 2.4 mmol) was added to an ice-cooled solution of the aminoalcohol (93) (0.20 g, 1.17 mmol) in anhydrous ether (10 ml) under an atmosphere of nitrogen. Excess ethereal diazomethane solution[24] was added and the resultant mixture stirred at 0-5° under nitrogen overnight. Aqueous sodium bicarbonate solution (10%) was added and the aqueous layer extracted twice with ether. The combined organic layers were dried and evaporated to give a colourless oil (78 mg) which corresponded by ^{1}H n.m.r. spectroscopy to unreacted (93).

Attempted O-methylation of the aminoalcohol (93) (diazomethane/silica)

The aminoalocohol (93) (0.20 g, 1.17 mmol) in anhydrous ether (4 ml) was added to a stirred suspension of Amicon Matrex silica (2 g) in anhydrous ether (10 ml) under a nitrogen atmosphere. After stirring for 5 min, excess of ethereal diazomethane solution[24] was added and the resultant mixture stirred under nitrogen at room temperature overnight. The silica was filtered off and extracted twice with ether. The combined ethereal solutions were evaporated to yield and oil (0.12 g) which corresponded by ^{1}H n.m.r. spectroscopy and mass spectrometry to a mixture of (93) and desired product (94) in approximately equal proportions as indicated by integration of the ^{1}H n.m.r. spectrum which included additional singlets at δ 3.3 and 3.85 and an additional peak appeared at *m/z* 185 in the mass spectrum.

Attempted O-methylation of the aminoalcohol (93) (methyllithium/iodomethane)

Ethereal methyllithium (1.3 M, 1.12 ml, 1.46 mmol) was added to an ice-cooled solution of the aminoalcohol (93) (0.25 g, 1.46 mmol) in anhydrous ether (15 ml) under an atmosphere of nitrogen. After stirring for 10 min, iodomethane (0.23 g, 1.61 mmol) in anhydrous ether (3 ml) was slowly added and the resulting mixture stirred under nitrogen at 0-5° for 1 h. The mixture was quenched with saturated aqueous layer extracted twice with ether. The combined organic layers were washed with brine, dried and evaporated to

yield a brown oil (0.15 g) which corresponded by ^{1}H n.m.r. spectroscopy to unreacted (93).

1-Methoxyprop-2-yne (11)

Prepared by the procedure of Vincens et al[25], b.p. 59-62°, (lit.[25] 61-62°). ν_{max} (film) 3300 (C=C–H), 2200 (C=C), 1100 cm^{-1} (C–O). ^{1}H n.m.r. δ ($CDCl_3$) 2.45, t, *J* 2 Hz, C≡C–H; 3.4, s, CH_3O; 4.1, d, *J* 2 Hz, CH_2. Mass spectrum *m/z* 70 (M, 6%), 69 (50), 55 (14), 53 (13), 39 (100).

1-Dimethylamino-4-methoxybut-2-yne (12)

Synthesized by modifying the procedure of Salvador and Simon[15] . Thus, aqueous formaldehyde solution (34%, 20.2 ml, 0.23 mol) and 1-methoxyprop-2-yne (11) (10 g, 0.143 mol) in methanol (25 ml) were added to aqueous dimethylamine solution (26%, 29.5 ml, 0.17 mol) which had been brought to pH9 by the addition of 50% sulphuric acid. Anhydrous cupric sulphate (0.8 g) in water (10 ml) was added and the pH adjusted to 8 with excess dimethylamine solution. The resulting mixture was heated under reflux for 40 h, cooled, poured into concentrated, aqueous ammonia (30%, 200 ml) and extracted thrice with dichloromethane. The combined organic layers were washed with brine, dried and evaporated to give the *amine* (12) (12.15 g, 67%) as a brown oil, b.p. 72-75°/17 mm (Found: C, 65.5; H, 10.2.

$C_7H_{13}NO$ requires C, 66.1; H 10.3%). ν_{max} (film) only C–H absorptions (2750-2980 cm^{-1}) above 1500 cm^{-1}. ^1H n.m.r. δ ($CDCl_3$) 2.35, s, $N(CH_3)_2$; 3.33, t, *J* 2 Hz, CH_2N; 3.42, s, CH_3O; 4.2, t, *J* 2 Hz, CH_2O. Mass spectrum *m/z* 127 (M, 80%), 126 (77), 112 (23), 96 (48), 94 (56), 82 (100).

(E)-N, N-*Dimethyl*-N-*(3-methoxymethyl-2-hepten-1-yl)amine (94)*

Anhydrous benzene (500 ml) was added to a stirred solution of butylmagnesium bromide (0.393 mol) in anhydrous ether (500 ml) under an atmosphere of nitrogen. The ether was distilled off, the methoxyaminoalkyne (12) (20.0 g, 0.158 mol) in benzene (30 ml) slowly added and the mixture heated at reflux for 7 h under nitrogen. The mixture was quenched with saturated, aqueous ammonium chloride solution, basified with saturated, aqueous sodium bicarbonate solution and the combined aqueous layers extracted thrice with ether. The combined organic layers were washed with brine, dried and evaporated to give the *alkene* (94) (15.33 g, 52%) as a yellow oil, b.p. 106-110°/20 mm (Found: C, 71.4; H, 12.4. $C_{11}H_{23}NO$ requires C, 71.3; H, 12.5%). ν_{max} (film) only C–H absorptions (2750-2950 cm^{-1}) above 1500 cm^{-1}. ^1H n.m.r. δ ($CDCl_3$) 0.7-1.6, br, $CH_3CH_2CH_2$; 2.1, m, $C{=}C{-}CH_2$; 2.25, s, $N(CH_3)_2$; 3.0, d, *J* 7 Hz, CH_2N; 3.3, s, CH_3O; 3.85, s, CH_2O; 5.55 t, *J* 7 Hz, C=C–H. Mass spectrum *m/z* 185 (M, 23%), 1.54 (19), 140 (10), 93 (25), 79 (58), 58 (100).

The amine (94) was also obtained (in similar yield) via reaction with 4 equivalents of the Grignard reagent under the conditions described above.

Other previous runs of this reaction, except using less vigorous conditions, provided the following results:-

(i) stirring with 4 equivalents of Grignard reagent in (a) ether at room temperature for 22 h, (b) ether with heating under reflux for 30 h, (c) tetrahydrofuran at room temperature for 3 h or (d) tetrahydrofuran with heating under reflux for 12 h returned a product corresponding by ^{1}H n.m.r. spectroscopy to unreacted (12).

(ii) reaction with 1.3 equivalents of Grignard reagent in benzene at reflux for (a) 90 min and (b) 7 h, gave products having, in additon to the infrared absorptions and ^{1}H n.m.r. signals due to (12) and (94), an absorption at 1960 cm^{-1} in the infrared spectra and multiplets at δ 2.9 and 4.7 plus a singlet at δ 2.2 in the ^{1}H n.m.r. spectra.

(E)-*1-Chloro-3-methoxymethylhept-2-ene (95)*

Prepared by adapting the method of Mornet and Gouin[13] . Thus, the allylic amine (94) (6.50 g, 35 mmol) in benzene (40 ml) was added dropwise to an ice-cooled, stirred mixture of ethyl chloroformate (37.90 g, 0.35 mol), potassium carbonate (3.60 g) and benzene (100 ml) under an atmosphere of nitrogen. After being allowed to warm to room temperature, the mixture was stirred under nitrogen for 4 h. After filtration, the benzene and carbamate by-product were removed by distillation under reduced pressure to leave the

chloride (95) (5.01 g, 81%) as a yellow oil, b.p. 30-32°/0.02 mm. Found: *m/z* 176.0985. $C_9H_{17}ClO$ requires 176.0968. ν_{max} (film) only C–H absorptions (2750-2950 cm^{-1}) above 1500 cm^{-1}.. ^1H n.m.r. δ ($CDCl_3$) 0.7-1.6, br, $CH_3CH_2CH_2$; 2.1, m, $C{=}C{-}CH_2$; 3.3, s, CH_3O; 3.9, s, CH_2O; 4.1, d, *J* 8 Hz, CH_2Cl; 5.65, t, *J* 8 Hz,C=C–H. Mass spectrum *m/z* 176 (3%)/178 (M, 1), 141 (47), 121 (22), 119 (95), 114 (17), 109 (15), 85 (33), 41 (100).

2-Acetyl-γ-butyrolactone (102)

Prepared by modifying the procedure of Johnson[27]. Thus, ethyl acetoacetate (101) (200.00 g, 1.53mol) was added portionwise to a mixture of sodium hydroxide (61.54 g, 1.53 mol), water (570 ml) and ethanol (180 ml) at 0°. After stirring for 30 min at 0°, ethylene oxide (83.00 g, 1.88 mol) was added portionwise at 0°. The resulting mixture was stirred at 0-5° for 72 h. Acetic acid (100 g, 1.68 mol) was added, the mixture saturated with sodium chloride and extracted thrice with dichloromethane. The combined organic layers were dried and evaporated yielding a pink oil which was distilled under reduced pressure to give the *lactone* (102) (93.00 g, 47%) as a colourless liquid, b.p. 135-140°/18 mm (lit.[27] 107-108°/5 mm). ν_{max} (film) 1770 (lactone C=O), 1720 cm^{-1} (ketone C=O). ^1H n.m.r.[68]. Mass spectrum *m/z* 128 (M, 30%), 113 (23), 86 (100).

2-Acetyl-2-methyl-γ-butyrolactone (103)

Synthesized by modifying the procedure of Stepanov and Smirnov[28]. Thus, 2-acetyl-γ-butyrolactone (102) (76.8 g, 0.6 mol) in anhydrous benzene (420 ml) was added to a stirred suspension of sodium metal (16.0 g, 0.7mol) in anhydrous benzene (600 ml) containing methanol (3 ml) under an atmosphere of nitrogen. The mixture was sirred overnight, then warmed (infrared lamp) with stirring for 3 h, under nitrogen. Methyl iodide (102 ml, 231.5 g, 1.6 mol) was added, the mixture heated under reflux for 3 h and stood at room temperature overnight under nitrogen. The mixture was quenched with water and the aqueous layer extracted twice with ether then twice with dichloromethane. The combined organic layers were dried and evaporated to give a yellow oil which was distilled under reduced pressure to provide the *methylated lactone* (103) (72.50 g, 85%) as a colourless liquid, b.p. 120-122°/15 mm (lit.[28] 125-126°/18 mm). ν_{max} (film) 1766 (lactone C=O), 1712 cm^{-1} (ketone C=O). ^1H n.m.r.[68]. Mass spectrum *m/z* 142 (M, 1%), 141(1), 100 (17), 58 (100).

5-Chloro-3-methylpentan-2-one (104)

Synthesized by adapting the procedure of Cannon, Ellis and Leal[29]. Thus, a mixture of concentrated hydrochloric acid (72 ml), water (85 ml) and 2-acetyl-2-methyl-γ-butyrolactone (103) (61.44 g, 0.43 mol) were placed in a short-path distillation apparatus and carefully heated until all gas evolution had ceased. The distillation was commenced and distillate (150 ml) collected.

Water (75 ml) was added and further distillate (50 ml) collected. The aqueous layer of the distillate was extracted twice with ether. The combined organic layers were dried with calcium chloride for 90 min and evaporated to give the *chloroketone* (104) (44.50 g, 77%) as a pale yellow oil, which was used without further purification. A small portion was distilled under reduced pressure, b.p. 70°/19 mm. ν_{max} (film) 1714 cm^{-1} (C=O). ^1H n.m.r. δ ($CDCl_3$) 1.15, d, *J* 7 Hz, CH_3, 1.5-2.2, m, CH_2; 2.2, s, CH_3CO; 2.9, m, CH; 3.6, t, *J* 7 Hz, CH_2 Cl. Mass spectrum *m/z* 135 (5%)/137 (M+1, 2), 118 (2)/120(1), 98 (13), 72 (33), 55 (23), 43 (100).

Methyl 1-methylcyclopropyl ketone (105)

Synthesized by modifying the procedure of Cannon, Ellis and Leal[29]. Thus, the chloride (104) (220.0 g, 1.64 mol) was added slowly to a stirred solution of sodium hydroxide (101.3 g, 2.52 mol) in water (130 ml). The mixture was heated under reflux for 2.5 h. Water (230 ml) was added and the mixture was heated under reflux for an additional 90 min. A water-ketone mixture was distilled until all the organic layer was removed from the reaction mixture. The product layer of the distillate was separated and the aqueous layer saturated with potassium carbonate. The saturated aqueous layer was extracted with ether (2 x 150 ml) and the combined organic layers dried over calcium chloride. The dried ether solution was fractionally distilled to give the *cyclopropylketone* (105) (120.7 g, 75%) as a colourless liquid, b.p. 121-124° (lit.[26] 125-127°). ν_{max} (film) 1692 cm^{-1} (C=O). ^1H n.m.r.[68] δ ($CDCl_3$) 0.65, m,

CH_2; 1.15, m, CH_2; 1.35, s, CH_3; 2.05, s, CH_3CO. Mass spectrum *m/z* 99 (M+1, 26), 98 (M, 26), 83 (13), 55 (30), 43 (100).

Dimethyl (1-methylcyclopropyl) carbinol (106)

The cyclopropyl ketone (105) (20.00 g, 0.20 mol) in anhydrous ether (200 ml) was slowly added to a stirred solution of methylmagnesium iodide (0.30 mol) in anhydrous ether (450 ml) under an atmosphere of nitrogen. The resulting mixture was heated under reflux for 2 h then quenched with saturated, aqueous ammonium chloride solution. The aqueous layer was extracted twice with ether and the combined organic layers dried and fractionally distilled to give the *carbinol* (106) (17.01 g, 74%) as a colourless liquid, b.p. 132-134° (lit.[26] 132-133°). ν_{max} (film) 3150-3650 cm^{-1} (OH), only C–H absorptions between 3100 and 1500 cm^{-1}. ^1H n.m.r. δ ($CDCl_3$) 0.15, m, CH_2; 0.6, m, CH_2; 1.1, s, CH_3; 1.2, s, $(CH_3)_2$; 1.3 (varies with sample concentration), br, OH. Mass spectrum *m/z* 114 (M, <1%), 99 (5), 97 (2), 86 (41), 71 (45), 59 (46), 43 (100).

5-Bromo-2,3-dimethylpent-2-ene (99)

The carbinol (106) (72.0 g, 0.63 mol) in dichloromethane (120 ml) was shaken with aqueous hydrogen bromide solution (48%, 250 ml) in a separating funnel for 5 min. The aqueous layer was extracted twice with

dichloromethane and the combined organic layers washed with saturated aqueous sodium carbonate solution until the washings remained basic, then dried and evaporated to give the *bromide* (99) (92.0 g, 82%) as a dark green oil, b.p. 70-78°/26 mm (lit.[26] 50-51°/10 mm). ν_{max} (film) only C–H absorptions above 1500 cm^{-1}. ^1H n.m.r. δ ($CDCl_3$, 300 MHz) 1.65, s, CH_3; 1.67, s, $(CH_3)_2$; 2.60, t, *J* 8.1 Hz, CH_2–C=C; 3.35, t, *J* 8.1 Hz, CH_2Br. ^{13}C n.m.r. δ ($CDCl_3$, 75.47 MHz) 18.19, 20.26, 20.58, CH_3–C=C; 31.00, CH_2–C=C; 38.31, C-Br; 124.66, 127.79, C=C . Mass spectrum *m/z* 176/178 (M, 31%), 97 (51), 83 (59), 55 (91), 40 (100).

Attempted synthesis of* (E)-N,N-*Dimethyl*-N-*(6,7-dimethyl-3-methoxymethyl) octa-2,6-dien-1-ylamine (10)

(a) The bromide (99) (0.87 g, 4.92 mmol) in anhydrous ether (4 ml) was slowly added to a stirred mixture of magnesium turnings (0.12 g, 4.92 mmol), a few crystals of iodine and anhydrous ether (5 ml) under an atmosphere of nitrogen with warming to initiate the reaction. The resulting mixture was refluxed for 30 min, cooled to room temperature and anhydrous benzene (9 ml) was added. The ether was distilled off, the mixture cooled to room temperature and the methoxyaminoalkyne (12) (0.25 g, 1.96 mmol) in anhydrous benzene (3 ml) added. The resulting mixture was heated under reflux for 7 h under an atmosphere of nitrogen, quenched with saturated, aqueous ammonium chloide solution and the pH adjusted to 8 with saturated, aqueous sodium bicarbonate solution. The aqueous layer was extracted twice with ether and the combined organic layers washed with

brine, dried and evaporated to yield a brown oil which was chromatographed on a silica squat column. Elution with hexane containing increasing proportions of dichloromethane gave *2,3,8,9-tetramethyl-2,8-decadiene* (107) as a colourless oil, b.p. 45-46°/0.05 mm. Found: *m/z* 194.2044. $C_{14}H_{26}$ requires 194.2035. ν_{max} (film) 2924, 2856, 1456, 1374, 1154 cm^{-1}. ^1H n.m.r. δ ($CDCl_3$) 1.35, m, CH_2; 1.65, s, CH_3; 2.1, m, C=C–CH_2. Mass spectrum *m/z* 194 (M, 7%), 110 (12), 95 (13), 83 (10), 55 (11), 41 (13), 28 (100). Further elution with increasing proportions of methanol in dichloromethane gave a yellow oil. Found: *m/z* 224.1899. $C_{13}H_{24}N_2O$ requires 224.1889. ν_{max} (film) 2700-2900, 1960, 1450 cm^{-1}. ^1H n.m.r. δ ($CDCl_3$) 1.65, s; 2-2.5, br 2.15, m; 2.3, s; 2.35, s; 2.95, m; 3.33, t, *J* 2 Hz; 3.42, s; 4.2, t, *J* 2 Hz; 4.75, m. Mass spectrum *m/z* 224, 210, 208, 193, 180, 178, 154, 148, 137, 133, 123, 119, 110, 83.

Repeat reactions with the following differences:- (i) refluxing in benzene for 90 min, (ii) refluxing in ether for 90 min and (iii) refluxing in ether overnight provided the same product mixture.

(b) The bromide (99) (0.87 g, 4.92 mmol) in anhydrous ether (4 ml) was slowly added to a mixture of magnesium turnings (0.12 g, 4.92 mmol), a few crystals of iodine, the methoxyaminoalkyne (12) (0.25 g, 1.96 mmol) and anhydrous ether (9 ml) with warming under an atmosphere of nitrogen. The resulting mixture was heated at reflux under nitrogen for 5.5 h. Saturated, aqueous ammonium chloride solution was added and the pH adjusted to 8 with saturated, aqueous sodium bicarbonate solution. The aqueous layer was extracted twice with ether, the combined organic layers washed with brine, dried and evaporated to give a yellow oil corresponding by ^1H n.m.r. spectroscopy to a mixture of starting materials (99) and (12).

4,5-Dimethyl-1-phenylhex-4-en-1-ol (110)

A solution of the bromide (99) (0.44 g, 2.46 mmol) in anhydrous ether (2 ml) was slowly added to a mixture of magnesium turnings (0.06 g, 2.46 mmol), a crystal of iodine and anhydrous ether (2.5 ml) under an atmosphere of nitrogen. The resulting mixture was heated at reflux under nitrogen for 30 min. After cooling to room temperature, benzaldehyde (0.21 g, 2 mmol) in anhydrous ether (1.5 ml) was added dropwise and the mixture heated at reflux under nitrogen for 3 h. Saturated, aqueous ammonium chloride solution was added and the aqueous layer extracted twice with ether. The combined organic extracts were washed with brine, dried and evaporated to yield a pale yellow oil which was flash chromatographed on silica gel. Elution with 30% ether in hexane provided the *benzylic alcohol* (110) (0.25 g, 61%) as a colourless oil, b.p. 70°/0.007 mm (Found: C, 82.5; H 9.7 $C_{14}H_{20}O$ requires C, 82.3; H, 9.9%). ν_{max} (film) 3368 (OH), 1496, 1456 (Ar), 1060 (C–O), 762, 702 cm^{-1} (Ar-H). ^1H n.m.r. δ ($CDCl_3$, 300 MHz) 1.61, s, CH_3; 1.62, s, CH_3; 1.71-1.85, m, CH_2–C–O; 1.99-2.16, m, CH_2–C=C; 4.61, dd, *J* 7.65, 5.40 Hz; CH–O; 7.21-7.44, m, ArH. ^{13}C n.m.r. δ ($CDCl_3$, 75.47 MHz) 18.20, 20.07, 20.58, CH_3–C=C; 30.75, CH_2–C–O; 37.34, CH_2–C=C; 74.54, C–O; 124.62, 127.08, C=C; 125.85, 127.40, 128.37, 144.80, Ar. Mass spectrum *m/z* 204 (M, 15%), 186 (26), 171 (47), 143 (50), 133 (46), 120 (100).

Attempted preparation of (E)*-6,7-Dimethyl-3-hydroxymethylocta-2,6-dien-1-ol (112)*

2-Butyne-1,4-diol (111) (0.114 g, 1.33 mmol) in anhydrous tetrahydrofuran (4 ml) was slowly added to a stirred solution of the Grignard reagent (100) (prepared as before) (5.30 mmol) in anhydrous ether (9 ml) at room temperature under an atmosphere of nitrogen. The resulting mixture was heated at reflux under nitrogen for 4 h then quenched with hydrochloric acid (10%). The aqueous layer was extracted thrice with ether and the combined organic layers were washed with brine, dried and evaporated to give a pale yellow oil corresponding by ^{1}H n.m.r. spectroscopy to a mixture of dimerized Grignard reagent (107) and starting diol (111).

(E)*-5,6-Dimethyl-2-(2-*N,N*-dimethylaminoethylidene)hept-5-en-1-ol (9)*

A solution of the bromide (99) (15.04 g, 84.8 mmol) in anhydrous ether (50 ml) was slowly added to a mixture of mangesium turnings (2.08 g, 84.8 mmol), iodine (a few crystals) and anhydrous ether (50 ml) under an atmosphere of nitrogen with slight warming. The mixture was heated under reflux for 30 min, cooled to room temperature, then the substrate alkyne (8) (2.40 g, 21.28 mmol) in anhydrous ether (30 ml) was slowly added. The resulting mixture was stirred at room temperature under an atmosphere of nitrogen for 5 h. Saturated, aqueous, ammonium chloride solution was added and the aqueous layer extracted twice with ether . The combined organic layers were washed with brine, dried and evaporated to yield a pale yellow oil which was

fractionally distilled under reduced pressure to provide the *dimer* (107) and the *alcohol* (9) (2.95 g, 66%) as a colourless liquid, b.p. 102-104°/0.01 mm. ν_{max} (film) 3200-3400 (OH), 1680 cm^{-1} (w) (C=C). ^1H n.m.r. δ ($CDCl_3$) 1.65, s, CH_3–C=C; 2.05-2.35, m, C=C–CH_2CH_2–C=C; 2.25, s, $N(CH_3)_2$; 2.95, d, *J* 7 Hz, CH_2N; 3.35 (varies with sample concentration), br, OH; 4.1, s, CH_2O; 5.6, t, *J* 7 Hz, C=C–H. ^{13}C n.m.r. δ ($CDCl_3$, 20.1 MHz) 18.3, q, 19.9, q, 20.4, q, CH_3–C=C; 26.7, t, 33.5, t, CH_2–C=C; 45.2, q, $N(CH_3)_2$; 56.5, t, CH_2N; 66.1, t, CH_2O; 122.1, d, CH; 122.4, s, 123.9, s, 127.3, s, C=C. Mass spectrum *m/z* 211 (M, 6%), 180 (16), 166 (11), 140 (13), 127 (9), 86 (42), 84 (65), 49 (100). MIKES (*m/z* 211) 182, 180, 166, 140, 127. Trace impurities, detected by spectroscopy, which could not be removed by distillation or chromatography, prevented a satisfactory microanalysis being obtained. However, the corresponding silyl ethers (115) and (116) were obtained analytically pure.

Sequential reaction of aminobutynol (8) with methylmagnesium iodide and butylmagnesium bromide

(a) Aminobutynol (8) (0.25 g, 2.21 mmol) in anhydrous ether (4 ml) was added dropwise to a stirred solution of methylmagnesium iodide (2.43 mmol) in anhydrous ether (5 ml) under a nitrogen atmosphere and the resulting mixture stirred at room temperature for 20 min. The alkoxide mixture was then added dropwise via syringe to a stirred solution of butylmagnesium bromide (2.87 mmol) in anhydrous ether (5 ml) under nitrogen and the resultant mixture stirred at room temperature overnight. The mixture was quenched by the addition of saturated, aqueous, ammonium chloride

solution. The aqueous layer was extracted twice with ether and the combined organic layers dried and evaporated to yield a yellow oil (0.10 g) which corresponded by ^{1}H n.m.r. spectroscopy to a mixture of (93) and (8) in the ratio 3:5.

(b) In a procedure identical to (a) above, except using a solution of methylmagnesium iodide (4.86 mmol) in anhydrous ether (7 ml), a yellow oil (0.14 g) corresponding by ^{1}H n.m.r. spectroscopy to a mixture of (93) and (8) in the ratio 5:7 was obtained.

(c) In a procedure identical to (b) above, except using a solution of butylmagnesium bromide (5.53 mmol) in anhydrous ether (7 ml), a yellow oil (0.20 g) corresponding by ^{1}H n.m.r. spectroscopy to a mixture of (93) and (8) in the ratio 18:5.

Attempted O-methylation of the aminoalcohol (9) (sodium hydride/iodomethane/tetrahydrofuran)

The amino alcohol (9) (0.100 g, 0.47 mmol) in anhydrous tetrahydrofuran (5 ml) was added slowly to a stirred suspension of sodium hydride (80% dispersion in paraffin oil, 0.025 g, 0.75 mmol) in anhydrous tetrahydrofuran (20 ml) under an atmosphere of nitrogen. The resulting mixture was stirred under nitrogen at room temperature for 20 min. Iodomethane (0.073 g, 0.52 mmol) in anhydrous tetrahydrofuran (5 ml) was added and the resulting mixture stirred at room temperature under nitrogen for 60 h. Saturated,

aqueous, ammonium chloride solution was added and the aqueous layer extracted thrice with dichloromethane. The combined organic layers were dried and evaporated to give a brown oil (0.100 g). ^{1}H n.m.r. δ ($CDCl_3$) 0.9, m; 1.3, m; 1.65, s; 2.05-2.45, m; 2.65, m; 3.45, s; 3.55, s; 4.0, s; 4.25, d, *J* 8 Hz; 5.7, t, *J* 8 Hz. Mass spectrum *m/z* 297, 279, 255, 240, 211, 180, 149.

Attempted O-methylation of the aminoalcohol (9) (methyllithium/iodomethane)

Ethereal methyllithium (1.3 M, 0.55 ml, 0.71 mmol) was added to an ice-cooled, stirred solution of the aminoalcohol (9) (0.150 g, 0.71 mmol) in anhydrous ether (12 ml) under an atmosphere of nitrogen. After stirring for 10 min at 0-5°, iodomethane (0.11 g, 0.78 mmol) in anhydrous ether (3 ml) was added and the resulting mixture stirred under nitrogen at 0-5° for 1 h. Saturated, aqueous ammonium chloride solution was added and the aqueous layer extracted twice with ether. The combined organic layers were dried and evaporated to yield a yellow oil which was microdistilled in a sublimator block to give a colourless liquid corresponding by ^{1}H n.m.r. spectroscopy to starting material (9).

Attempted O-methylation of the aminoalcohol (9) (sodium hydride/iodomethane)

Sodium hydride (80% dispersion in paraffin oil, 0.16 g, 5.33 mmol) was added from a Gooch tube to a stirred solution of the amino alcohol (9) (0.92 g, 4.33 mmol) in anhydrous tetrahydrofuran (5.5 ml) at room temperature under an atmosphere of nitrogen. The resulting mixture was stirred at room temperature for 1 h. Dimethyl sulphate (0.41 ml, 0.55 g, 4.33 mmol) was added and the mixture stirred at room temperature under nitrogen for a further 1 h. The mixture was quenched with ethanol (4 ml) and diluted with water (4 ml). The pH was adjusted to 9 with hydrochloric acid (5%) and the mixture extracted thrice with dichloromethane. The combined organic extracts were dried and evaporated to yield a brown oil (1.01 g). ^{1}H n.m.r. δ 0.9, m; 1.3, m; 1.65, s; 2.0-2.3, m; 2.1, s; 2.2, s; 2.9, d, *J* 7 Hz; 3.25, s; 3.3, s; 3.55 (varies with sample concentration), s; 3.8, s; 3.95, s; 4.2, d, *J* 8 Hz; 5.45, t, *J* 7 Hz. 5.7, t, *J* 8 Hz.

A portion of the above sample was microdistilled in a sublimator block. ^{1}H n.m.r. δ 1.65, s; 2.1, s; 2.1-2.3, m; 2.2, s; 2.9, d, *J* 7 Hz; 3.25, s; 3.4 (varies with sample concentration), br; 3.8, s; 3.95, s; 5.45, t, *J* 7 Hz. Mass spectrum *m/z* 225, 211, 197, 196, 194, 180, 166, 154, 140.

An analogous reaction carried out using similar conditions except halving the molar equivalents of dimethyl sulphate provided a similar product mixture.

(E)-N,N-*Dimethyl*-N-*(6,7-dimethyl-3-trimethylsilyloxymethyl)octa-2,6-dien-1-yl amine (115)*

Chlorotrimethylsilane (0.258 g, 2.38 mmol) in anhydrous tetrahydrofuran (5 ml) was slowly added to a stirred mixture of the alcohol (9) (0.457 g, 2.17 mmol), triethylamine (0.115 g, 1.14 mmol) and tetrahydrofuran (14 ml) at room temperature under an atmosphere of nitrogen. The resulting mixture was stirred at room temperature under nitrogen for 27 h. Water (15 ml) was added, followed by dichloromethane (15 ml) and the layers separated. The aqueous layer was extracted twice with dichloromethane and the combined organic extracts washed with saturated, aqueous, sodium bicarbonate solution, dried and evaporated to yield the *title compound* (0.541 g, 88%) as a yellow oil which was microdistilled in a sublimator block, b.p. 65°/0.01 mm (Found: C, 67.6; H, 11.4. $C_{16}H_{33}NOSi$ requires C, 67.8; H, 11.7%) ν_{max} (CH_2Cl_2) 2956, 2856, 2820, 2772 (C–H), 1460 (C=C), 1120, 1090, 1056, 1018, 874, 842 cm^{-1}. ^1H n.m.r. δ ($CDCl_3$) 0.15, s, $Si(CH_3)_3$; 1.65, s, C=C–CH_3; 2.0-2.35, m, C=C–CH_2CH_2–C=C; 2.25, s, $N(CH_3)_2$; 2.95, d, *J* 7 Hz, CH_2N; 4.1, s, CH_2O; 5.5, t, *J* 7 Hz, C=C–H. Mass spectrum *m/z* 283 (M, 26%), 269 (16), 211 (24), 199 (37)), 180 (100), 166 (42), 142 (21) 133 (63), 73 (87), 58 (95).

(E)-N,N-*Dimethyl*-N-*(6,7-dimethyl-3*-tert.-*butyldimethylsilyloxymethyl)octa-2,6-dien-1-yl amine (116)*

Chloro*tert.*-butyldimethylsilane (0.366 g, 2.44 mmol) in anhydrous tetrahydrofuran (5 ml) was slowly added to a stirred mixture of the alcohol (9)

(0.467 g, 2.21 mmol), triethylamine (0.269 g, 2.65 mmol), 4-dimethylaminopyridine (0.014 g, 0.11 mmol) and anhydrous tetrahydrofuran (18 ml) at room temperature under an atmosphere of nitrogen. The resulting mixture was stirred at room temperature under nitrogen for 27 h. Water (15 ml) was added, followed by dichloromethane (15 ml). The aqueous layer was extracted twice with dichloromethane and the combined organic extracts were washed with saturated, aqueous, sodium bicarbonate solution, dried and evaporated to yield the *title compound* (0.668 g, 93%) as a yellow oil which was microdistilled in a sublimator block, b.p. 70°/0.01 mm (Found: C, 70.0; H, 12.1. $C_{19}H_{39}NOSi$ requires C, 70.1; H, 12.1%). ν_{max} (CH_2Cl_2) 2932, 2856, 2772, (C–H), 1466 (C=C), 1124, 1092, 1062, 838 cm^{-1}. ^1H n.m.r. δ ($CDCl_3$) 0.0, s, $SiMe_2$; 0.85, s, $SiC(CH_3)_3$; 1.65, s, C=C–CH_3; 1.95-2.3, m, C=C–CH_2CH_2–C=C; 2.2, s, $N(CH_3)_2$; 2.9, d, *J* 7 Hz, CH_2N; 4.05, s, CH_2O; 5.5, t, *J* 7 Hz, C=C–H. Mass spectrum *m/z* 325 (M, 31%), 254 (18), 241 (16), 223 (7), 209 (9), 180 (100), 166 (78), 141 (24), 133 (63).

An analogous reaction using dichloromethane as solvent, instead of tetrahydrofuran, provided (116) in 92% yield.

(E)-N,N-*Dimethyl*-N-(3- tert.-*butyldimethylsilyloxymethyl-2-hepten-1-yl) amine (119)*

Chlorodimethyl*tert.*-butylsilane (4.80 g, 32.1 mmol) in anhydrous tetrahydrofuran (50 ml) was slowly added to a stirred mixture of the alcohol (93) (5.00 g, 29.2 mmol), triethylamine (3.50 g, 35.0 mmol),

4-dimethylaminopyridine (0.18 g, 1.50 mmol) and anhydrous tetrahydrofuran (200 ml) at room temperature under an atmosphere of nitrogen. The resulting mixture was stirred at room temperature under nitrogen for 75 h. Water (40 ml) was added, followed by dichloromethane (250 ml). The aqueous layer was extracted with dichloromethane (15 ml) and the combined organic layers washed with saturated, aqueous, sodium bicarbonate solution, dried and evaporated to give the *title compound* (8.20 g, 98%) as a yellow oil which was microdistilled in a sublimator block, b.p. 70°/0.02 mm (Found: C, 67.6; H, 11.8. $C_{16}H_{35}NOSi$ requires C, 67.3; H, 12.4%). Found: *m/z* 285.2497. $C_{16}H_{35}NOSi$ requires 285.2488. ν_{max} (film) 2952, 2852, 2812, 2764, (C–H), 1464 (C=C), 1254, 1118, 1080, 1020, 836, 776 cm^{-1}. ^1H n.m.r. δ ($CDCl_3$) 0.0, s, $SiMe_2$; 0.7-1.5, br, $CH_3CH_2CH_2$; 0.85, s, $SiC(CH_3)_3$; 2.1, m, C=C–CH_2; 2.2, s, $N(CH_3)_2$; 2.9, d, *J* 7 Hz, CH_2N; 4.05, s, CH_2O; 5.5, t, *J* 7 Hz, C=C–H. Mass spectrum *m/z* 285 (M, 22%), 242 (3), 240 (5), 228 (3), 225 (2), 184 (56), 141 (26), 112 (10), 76 (92), 59 (50), 47 (100), 29 (52).

(E)-*1-Chloro-3-*tert.*-butyldimethylsilyloxymethylhept-2-ene (120)*

The silyloxyaminoalkene (5.89 g, 20.57 mmol) in benzene (50 ml) was added dropwise to an ice-cooled, stirred mixture of ethyl chloroformate (22.34 g, 0.21 mol), potassium carbonate (5.00 g) and benzene (300 ml) under an atmosphere of nitrogen. The mixture was stirred at 5° for 1.5 h, allowed to warm to ambient temperature and stirred for a further 2 h under nitrogen. The resulting mixture was filtered and evaporated. The residue was fractionally distilled under reduced pressure to yield the *chloride* (120) (3.96 g,

70%) as an unstable, colourless oil, b.p. 74-76°/0.03 mm. ν_{max} (CCl_4) 2956, 2928, 2856, 1472, 1256, 1120, 1086, 838 cm^{-1}. ^1H n.m.r. δ ($CDCl_3$) 0.05, s, $SiMe_2$; 0.7-1.5, br, $CH_2CH_2CH_3$; 0.9, s, $SiC(CH_3)_3$; 2.1, m, C=C–CH_2; 4.05, s, CH_2O, 4.1, d, *J* 8 Hz, CH_2Cl; 5.65, t, *J* 8 Hz, C=C–H. Mass spectrum *m/z* 276/278 (M, <1%), 261 (6)/263 (2), 241 (37), 219 (100).

(E)-2-*(2-Chloroethylidene)hex-1-yl ethyl carbonate (123)*

The allylic aminoalcohol (93) (0.50 g, 2.92 mmol) in benzene (5 ml) was added dropwise to an ice-cooled mixture of ethyl chloroformate (3.18 g, 29.2 mmol), potassium carbonate (1.00 g) and benzene (25 ml) under an atmosphere of nitrogen. The resulting mixture was allowed to warm to room temperature and stirred under nitrogen for 5 h. After filtration, the benzene and carbamate by-product were removed on a rotary evaporator to leave the *carbonate* (123) (0.524 g, 76%) as a yellow oil which was microdistilled in a sublimator block, b.p. 65°/0.01 mm (Found: C, 56.0; H, 8.1. $C_{11}H_{19}ClO_3$ requires C, 56.3; H, 8.2%). ν_{max} (film) 2956, 2868 (C–H), 1748 (C=O), 1262 cm^{-1} (C–O). ^1H n.m.r. δ 0.7-1.6, br, $CH_2CH_2CH_3$; 1.3, t, *J* 7 Hz, OCH_2CH_3; 2.15, m, C=C–CH_2; 4.05, d, *J* 8 Hz, CH_2Cl; 4.15, q, *J* 7 Hz, OCH_2CH_3; 4.5, s, CH_2O; 5.75, t, *J* 8 Hz, C=C–H. Mass spectrum *m/z* 234 (0.3%)/236 (M, 0.1), 199 (40), 109 (100).

CHAPTER 2

N-(2-Bromo-4-methylphenyl)-trifluoroacetamide (14)

Prepared by the procedure of Raner[10], m.p. 67.5-68° (lit.[10] 67-67.5°). ν_{max} (CCl_4) 3400 (NH), 1744 (C=O), 1610, 1584, 1532 (Ar), 1286, 1172, 1142 cm^{-1}. ^1H n.m.r. δ 2.35, s, CH_3; 7.15, dd, *J* 8, 2 Hz, ArH; 7.40, d, *J* 2 Hz, ArH; 8.25, d, *J* 8 Hz, ArH; 8.3, br, NH. Mass spectrum *m/z* 281/283 (M, 72%), 202 (100).

N-[2-Bromo-4-(trifluoroacetoxymethyl)-phenyl]-trifluoroacetamide (15)

Prepared by modifying the procedure of Raner[10]. A mixture of the toluidide (14) (18.67 g, 65.33 mmol), potassium persulphate (63.47 g, 0.23 mol), cupric carbonate (31.73 g, 0.26 mol) and trifluoroacetic acid (570 ml) were heated under reflux under a nitrogen atmosphere for 24 h. The trifluoracetic acid was removed by distillation and the residue extracted thrice with dichloromethane. The extract was washed with water, saturated, sodium bicarbonate solution, concentrated under reduced pressure, dried and evaporated to yield the *title compound* (21.33 g 83%). Recrystallization from hexane using decolourizing charcoal provided colourless crystals, m.p. 80-81° (lit.[10] 81-82°). ν_{max} (CCl_4) 3400 (NH), 2952 (C–H), 1788 (ester C=O), 1750 (amide C=O), 1610, 1586, 1532 (Ar), 1178, 1138 cm^{-1} (C-O). ^1H n.m.r. δ 5.3, s, OCH_2 ; 7.45, dd, *J* 8, 2 Hz, ArH; 7.7, d, *J* 2 Hz, ArH; 8.5, d, *J* 8 Hz, ArH; 8.5, br, NH. Mass spectrum *m/z* 393/395 (M, 100%), 314 (96), 280/282 (22).

N-*(2-Bromo-4-hydroxymethylphenyl)-trifluoroacetamide (16)*

Prepared by the procedure of Raner[10], m.p. 75.5-76° (lit.[10] 73-73.5°). ν_{max} (CH_2Cl_2) 3608 (OH), 3392 (NH), 1740 (C=O), 1608, 1586, 1536 (Ar), 1170 cm^{-1} (C–O). ^1H n.m.r. δ ($CDCl_3$) 2.45 (varies with sample concentration), br, OH; 4.7, s, CH_2O; 7.3, dd, *J* 8, 2 Hz, ArH; 7.6, d, *J* 2 Hz, ArH; 8.15, d, *J* 8 Hz, ArH; 8.5, br, NH. Mass spectrum *m/z* 297/299 (M, 28%), 280/282 (2), 268/270 (13), 218 (100).

N-*(2-bromophenyl)-trifluoroacetamide (125)*

Prepared by modifying the procedure of Raner[10]. Trifluoroacetic anhydride (65 ml, 96.6 g, 0.46 mol) was added dropwise over 15 min to a stirred solution of 2-bromoaniline (52.15 g, 0.30 mol) in dichloromethane (1400 ml) at room temperature under a nitrogen atmosphere. After stirring for 90 min at room temperature under nitrogen, the mixture was washed with saturated, aqueous, sodium bicarbonate solution (500 ml). The organic layer was dried and evaporated to give the *amide* (125) (79.0 g, 97%) as a white solid which was recrystallized from hexane, m.p. 61-61.5° (lit.[10] 69-70°). ν_{max} (CCl_4) 3400 (NH), 1750 (C=O), 1590, 1530 cm^{-1} (Ar). ^1H n.m.r. δ 6.9-7.6, m, ArH, 3H; 8.35, br, NH; 8.4, dd, *J* 8, 2 Hz, ArH. Mass spectrum *m/z* 267/269 (M, 82%), 198/200 (10), 188 (100), 170/172 (32), 168 (50), 155/157 (9), 143/145 (8), 119 (18), 102 (15), 91 (47).

N-[2-(3-Methylbut-2-en-1-yl)-phenyl]trifluoroacetamide (41)

Prepared by the procedure of Raner[10] to give a product identical to authentic material. ν_{max} (film) 3320 (NH), 1730 (C=O), 1610, 1590, 1540 cm^{-1} (Ar). ^1H n.m.r. δ 1.8, s, $C=C(CH_3)_2$; 3.35, d, *J* 7 Hz, $ArCH_2C=C$; 5.25, t, *J* 7 Hz, C=C–H; 7.2, m, 3H, ArH; 7.9-8.4, m, NH + ArH. Mass spectrum *m/z* 257 (M, 35%), 242 (12), 214 (4), 202 (16) 188 (10), 160 (17), 28 (100).

2-(3-Methylbut-2-en-1-yl)-aniline (30)

Prepared by the procedure of Raner[10]. b.p. 135-140°/13 mm (lit.[10] 130°/10 mm). ν_{max} (film) 3460, 3375 (NH), 1620 (C=C), 1590, 1500 cm^{-1} (Ar). ^1H n.m.r. δ ($CDCl_3$) 1.75, s, $C=C(CH_3)_2$; 3.2, d, *J* 7 Hz, $ArCH_2C=C$; 3.6 (varies with sample concentration), br, NH_2; 5.25, t, *J* 7 Hz, C=C–H; 6.5-7.4, m, ArH.

3-Iodo-2,2-dimethyl-1,2,3,4-tetrahydroquinoline (33)

Prepared by the procedure of Raner[10] to give a product identical to authentic material. ν_{max} (film) 3400 (NH), 1610, 1590 (Ar), 1495, 1485 cm^{-1}. ^1H n.m.r. δ ($CDCl_3$) 1.35, s, $C=C(CH_3)_2$; 3.5, d, *J* 7 Hz, CH_2; 3.7, br, NH; 4.4, dd, *J* 7, 8 Hz, CHI; 6.45-7.3, m, ArH. Mass spectrum *m/z* 288 (M+1), 273, 258, 243, 160, 145. Attempted distillation leads to decomposition[10].

N-*[2-(3-Methoxymethylhept-2-en-1-yl)-phenyl]trifluoroacetamide (126)*

Prepared by adapting the procedure of Raner[10]. A solution of trifluoroacetamide (125) (4.00 g, 14.96 mmol) in anhydrous tetrahydrofuran (200 ml) was cooled with stirring to −50° under an atmosphere of nitrogen. Ethereal methyllithium (1.4 M, 10.86 ml, 15.2 mmol) was added, followed by *tert.*-butyllithium in pentane (1.3 M, 25.85 ml, 33.6 mmol). After stirring for 1 min, *tetrakis*[iodo(tributylphosphine)copper(I)][33] (6.00 g, 14.96 mmol Cu) in anhydrous tetrahydrofuran (40 ml) was added, followed 5 min later by the allyllic chloride (95) (2.64 g, 14.96 mmol) in anhydrous tetrahydrofuran (25 ml). After stirring at −50° under nitrogen for a further 10 min, hydrochloric acid (5%, 200 ml) was added and the mixture extracted with ethyl acetate to give a yellow oil which was flash chromatographed on silica gel. Elution with 15% ethyl acetate in hexane provided the *allylbenzene* (126) (3.74 g, 76%) as a pale, yellow oil which was microdistilled under reduced pressure, b.p. 105°/0.025 mm (Found: C, 61.8; H, 6.8. $C_{17}H_{22}F_3NO_2$ requires C, 62.0; H, 6.7%). ν_{max} (film) 3300 (NH), 1720 (C=O), 1610, 1590, 1545 cm^{-1} (Ar). ^1H n.m.r. δ 0.7-1.6, br, $CH_2CH_2CH_3$; 2.15, m, C=C–CH_2; 3.25, s, OCH_3; 3.4, d, *J* 7 Hz, ArCH_2C=C; 3.8, s, CH_2O; 5.45, t, *J* 7 Hz, C=C–H; 7.2, m, ArH, 3H; 7.7-8.3, m, NH+ArH. Mass spectrum *m/z* 329 (M, < 1%), 298 (7), 297 (9), 255 (61), 240 (94), 202 (28), 142 (100).

2-(3-Methoxylmethylhept-2-en-1-yl)aniline (129)

The amide (126) (0.326 g, 0.99 mmol) dissolved in methanolic potassium hydroxide solution (10%, 12 ml) was heated under reflux for 5.5 h. Water (20 ml) was added and the mixture extracted with dichloromethane (3 x 30 ml). The combined organic layers were dried over anhydrous sodium sulphate and evaporated to give a yellow oil which was microdistilled in a sublimator block to yield the *allylaniline* (129) (0.221 g, 96%) as a colourless liquid, b.p. 100°/0.005 mm (Found: C, 77.0; H, 9.5. $C_{15}H_{23}NO$ requires C, 77.2; H, 9.9%). ν_{max} (film) 3464, 3368 (NH_2), 1624, 1604, 1584, 1500, (Ar, N–H), 1458, 1098 (C–O), 750 (ArH). ^{1}H n.m.r. δ 0.7-1.6, br, $CH_2CH_2CH_3$; 2.2, m, C=C–CH_2; 3.2, s, OCH_3; 3.25, d, *J* 7 Hz, $ArCH_2C$=C; 3.4, br, NH_2; 3.8, s, CH_2O; 5.5, t, *J* 7 Hz, C=C–H; 6.4-7.1, m, ArH. Mass spectrum *m/z* 233 (M, 20%), 201 (27), 188 (9), 186 (5), 172 (7), 158 (37), 144 (100), 118 (49), 106 (61).

(E)-2-(2-*Trifluoroacetamidophenyl*)*ethylidenehex-1-yl ethyl carbonate* (127)

A stirred solution of (125) (0.40 g, 1.50 mmol) in anhydrous tetrahydrofuran (20 ml) was cooled to −50° under an atmosphere of nitrogen. Ethereal methyllithium (1.4 M, 1.08 ml, 1.52 mmol) was added, followed by *tert*-butyllithium in pentane (1.3 M, 2.58 ml, 3.36 mmol). After stirring for 1 min, *tetrakis*[iodo(tributylphosphine)copper(I)][33] (0.60 g, 1.50 mmol) in anhydrous tetrahydrofuran (4 ml) was added, followed 5 min later by the allylic chloride (123) (0.36 g, 1.50 mmol) in anhydrous tetrahydrofuran (2 ml) after stirring at −50° under nitrogen for 15 min, the mixture was quenched

with hydrochloric acid (5%, 25 ml) and extracted with ethyl acetate to give a yellow oil which was flash chromatographed on silica gel. Elution with 15% ethyl acetate in hexane provided the *allylbenzene* (127) (0.37 g, 64%) as a colourless oil which was microdistilled under reduced pressure, b.p. 120°/0.01 mm (Found: C, 59.0; H, 6.0. $C_{19}H_{24}F_3NO_4$ requires C, 58.9; H, 6.2%). ν_{max} (CCl_4) 3368 (NH), 2960, 2868 (C–H), 1744 (amide C=O and carbonate C=O), 1592, 1530, 1458 cm^{-1} (Ar). ^1H n.m.r. δ 0.7-1.6, br, $CH_2CH_2CH_3$; 1.3, t, *J* 7 Hz, OCH_2 CH_3; 2.15, m, C=C–CH_2; 3.4, d, *J* 7 Hz, Ar–CH_2–C=C; 4.1, q, *J* 7 Hz, OCH_2CH_3; 4.5, s, CH_2O; 5.55, t, *J* 7 Hz, C=C–H; 7.1, m, ArH; 7.65-8.3, m, ArH+NH. Mass spectrum *m/z* 297 (5%), 255 (13), 240 (30), 216 (13), 189 (13), 142 (47), 32 (100).

(E)-N-[2-(3-tert.-*Butyldimethylsilyloxymethylhept-2-en-1-yl)phenyl]trifluoro-acetamide (128)*

A stirred solution of (125) (0.50 g, 1.86 mmol) in anhydrous tetrahydrofuran (25 ml) was cooled to −50° under an atmosphere of nitrogen. Ethereal methyllithium (1.2 M, 1.67 ml, 2 mmol) was added, followed by *tert*-butyllithium in pentane (2.0 M, 2 ml, 4 mmol). After stirring for 1 min, *tetrakis*[iodo(tributylphosphine)copper(I)][33] (0.75 g, 1.86 mmol) in anhydrous tetrahydrofuran (5 ml) was added, followed 5 min later by the allylic chloride (120) (0.52 g, 1.86 mmol) in anhydrous tetrahydrofuran (3 ml). After stirring at −50° under nitrogen for 15 min, the mixture was quenched with hydrochloric acid (5%, 40 ml) and extracted with ethyl acetate to yield a yellow oil which was flash chromatographed on silica gel. Elution with 7% ethyl

acetate in hexane afforded the *allylbenzene* (128) (0.18 g, 23%) as a pale yellow, unstable oil which was microdistilled under reduced pressure, b.p. 130°/0.01 mm. ν_{max} (CCl_4) 3352 (NH), 2956, 2856 (C–H), 1740 (C=O), 1592, 1532, 1458 cm^{-1} (Ar). ^1H n.m.r. δ 0.05, s, $SiMe_2$; 0.7-1.6, br, $CH_2CH_2CH_3$; 0.9, s, $SiC(CH_3)_3$; 2.15, m, C=C–CH_2; 3.4, d, *J* 7 Hz, Ar–CH_2–C=C; 4.1, s, CH_2O; 5.5, t, *J* 7 Hz, C=C–H; 7.1-7.5, m, ArH; 7.8-8.3, m, ArH + NH. Mass spectrum (electron impact) *m/z* 372 (42%), 241 (32), 212 (17), 132 (13), 95 (32), 91(23), 75(100), 68 (50), 57 (97). Mass spectrum (chemical ionization) *m/z* 430 (M+1, 2%), 372 (49), 299 (20), 298 (100), 254 (19), 219 (11).

Attempted preparation of 3-Iodo-2-butyl-2-methoxymethyl-1,2,3,4-tetrahydro-quinoline (130)

(a) A mixture of the allylaniline (129) (80 mg, 0.34 mmol), iodine (91 mg, 0.36 mmol), sodium carbonate (114 mg) and dichloromethane (6 ml) was stirred for 4 h at ambient temperature under an atmosphre of nitrogen. The mixture was washed with aqueous, sodium thiosulphate solution (10%, 8 ml) and the aqueous layer extracted twice with dichloromethane. The combined organic layers were dried (Na_2SO_4) and evaporated to give a brown, intractable oil. Attempts at chromatography only served to effect further decomposition.

Repetitions of the reaction, carried out (i) in darkness (reaction vessel covered with aluminium foil) and (ii) with two equivalents of iodine in darkness, provided similar results.

(b) A mixture of the allylaniline (129) (0.164 g, 0.70 mmol), iodine (0.36 g, 1.40 mmol), sodium carbonate (0.16 g) and dichloromethane (5 ml) was stirred for 30 min at 0° under nitrogen in darkness. The mixture was washed with aqueous, sodium thiosulphate solution (10%, 12 ml) and the aqueous layer extracted twice with dichloromethane. The combined organic layers were dried (Na_2SO_4) and evaporated to afford a yellow oil corresponding by ^1H n.m.r.spectroscopy to unreacted (129).

(c) A similar procedure to that of (b) above was used except the reaction was carried out for 1 h at room temperature. This resulted in isolation of a brown, intractable oil.

Attempted synthesis of amide (131) from (129)

A mixture of allylaniline (129) (116 mg, 0.50 mmol), iodine (133 mg, 0.52 mmol), sodium carbonate (170 mg) and dichloromethane (5 ml) was stirred at room temperature in darkness under a nitrogen atmosphere for 4 h. Excess of trifluoroacetic anhydride (0.5 ml) was added and the mixture stirred for a further 1 h. The mixture was washed with aqueous sodium thiosulphate solution (10%, 10 ml) and the aqueous layer extracted thrice with dichloromethane. The combined organic layers were dried and evaporated to give a yellow, viscous oil (215 mg) which was flash chromatographed on silica gel. Elution with 15% ether in hexane yielded four fractions:- (a) a yellow oil, ν_{max} (CCl_4) 2960, 2928, 2872, 1696, 1490, 1410, 1152 cm^{-1}. ^1H n.m.r. δ 0.6-1.8, br; 3.1-3.5, m; 3.35, s; 3.5, d, *J* 7 Hz; 4.6, dd, *J* 7, 8 Hz; 6.4-7.2, m, ArH. Mass

spectrum *m/z* 455, 440, 422, 421, 410, 340, 328, 314, 296, 214. (b) a yellow oil, whose infrared and ^{1}H n.m.r. spectra were poorly resolved, (c) a pale, yellow oil corresponding by t.l.c. and ^{1}H n.m.r. spectroscopy to compound (126) and (d) a yellow oil whose infrared, ^{1}H n.m.r. and mass spectra were highly complex, indicating a mixture of components.

Attempted synthesis of 3-bromo-2-butyl-2-methoxymethyl-1,2,3,4-tetrahydro-quinoline (132)

A solution of bromine in dichloromethane (1 M, 0.6 ml, 0.6 mmol) was added dropwise to a mixture of (129) (123 mg, 0.53 mmol), sodium carbonate (150 mg) and dichloromethane (5 ml) in darkness at 0° under an atmosphere of nitrogen. The resulting mixture was stirred in the dard at 0° for 30 min under nitrogen then washed with aqueous sodium thiosulphate solution (10%, 3 ml). The aqueous layer was extracted twice with dichloromethane. The combined organic layers were dried (Na_2SO_4) and evaporated to yield a yellow oil (180 mg). ^{1}H n.m.r. δ 0.7-1.6, br; 2.2 m; 3.0-3.4, m; 3.2, s; 3.4, s; 3.55, br; 3.8, br; 4.6, m; 5.5, t, *J* 7 Hz; 6.35-7.4, m. Mass spectrum *m/z* 311/313, 279/281, 233.

Attempted preparation of (131) from (126)

(a) A mixture of trifluoroacetamide (126) (0.20 g, 0.61 mmol), iodine (0.31 g, 1.22 mmol), sodium carbonate (0.15 g) and dichloromethane (6 ml) was stirred in darkness under nitrogen at ambient temperature for 4 h. The mixture was washed with aqueous sodium thiosulphate solution (10%) and the aqueous layer extracted twice with dichloromethane. The combined organic layers were dried and evaporated to yield unreacted (126).

(b) The conditions were analogous to those in (a) above, except saturated, aqueous sodium carbonate solution (4 ml) was used instead of solid sodium carbonate and the reaction was allowed to continue for 46 h. This returned starting material (126) also.

Ethyl 3-bromo-4-aminobenzoate (134)

Prepared by the procedure of Leulier and Dinet[34], m.p. 91-92° (lit.[34] 92°). ν_{max} ($CDCl_3$) 3508, 3408 (NH), 2984 (C–H), 1704 (C=O), 1618, 1506 (Ar), 1290, 1248 cm^{-1} (C–O). ^1H n.m.r. δ ($CDCl_3$) 1.35, t, *J* 7 Hz, OCH_2CH_3; 4.35, q, *J* 7 Hz, OCH_2CH_3; 4.5, br, NH; 6.75, d, *J* 8 Hz, ArH; 7.85, dd, *J* 8, 2 Hz, ArH; 8.2, d, *J* 2 Hz, ArH. Mass spectrum *m/z* 243/245 (M, 22%), 215/217 (11), 198/200 (50), 57 (100).

Ethyl 3-bromo-4-trifluoroacetamidobenzoate (135)

Trifluoroacetic anhydride (1.74 ml, 2.58 g, 12.29 mmol) was injected dropwise into a stirred solution of the amine (134) (2.00 g, 8.19 mmol) in dichloromethane (40 ml) at room temperture under an atmosphere of nitrogen. After stirring for 5 h, the mixture was washed with saturated, aqueous, sodium bicarbonate solution and the aqueous layer extracted once with dichloromethane. The combined organic layers were dried and evaporated to yield a white solid which was recrystallized from hexane to give the *trifluoroacetamide* (135) (2.24 g, 80%) as colourless crystals, m.p. 69.5-70° (Found: C, 38.8; H, 2.6. $C_{11}H_9BrF_3NO_3$ requires C, 38.9; H, 2.7%). ν_{max} (CCl_4) 3396 (NH), 2984 (C–H), 1754 (amide C=O), 1728 (ester C=O), 1602, 1584, 1532 (Ar), 1478, 1396, 1370, 1286, 1232, 1174, 1132, 1110 cm^{-1}. ^1H n.m.r. δ 1.4, t, *J* 7 Hz, OCH_2CH_3; 4.35, q, *J* 7 Hz, OCH_2CH_3; 8.0, dd, *J* 8, 2 Hz, ArH; 8.2, d, *J* 2 Hz, ArH; 8.55, d, *J* 8 Hz, ArH; 8.65, br, NH. Mass spectrum *m/z* 339/341 (M, 100%), 294/296 (94), 260 (57).

Attempted synthesis of Ethyl 3-(3-methoxymethylhept-2-en-1-yl)-4-trifluoroacetamidobenzoate (136)

A stirred solution of (135) (0.25 g, 0.74 mmol) in anhydrous tetrahydrofuran was cooled to −50° under an atmosphere of nitrogen. Ethereal methyllithium (1.2 M, 0.67 ml, 0.8 mmol) was added, followed by *tert*-butyllithium in pentane (2.0 M, 0.80 ml, 1.6 mmol). After stirring for 1 min, *tetrakis*[iodo(tributylphosphine)copper(I)][33] (0.30 g, 0.74 mmol) in

anhydrous tetrahydrofuran (2 ml) was added, followed 5 min later by the allylic chloride (95) (0.13 g, 0.74 mmol) in anhydrous tetrahydrofuran (1 ml). After stirring at −50° under nitrogen for 15 min, the mixture was quenched with hydrochloric acid (5%, 15 ml) and extracted with ethyl acetate to yield a brown, intractable mixture.

CHAPTER 3

Methoxyacetyl chloride (139)

Prepared by the method of Stadlwieser[37], b.p. 109-113° (lit.[37] 105-110°). ν_{max} (film) 1800 (C=O), 1202, 1134 (C–O), 754 cm^{-1} (C–Cl). ^1H n.m.r. δ 3.5, s, CH_3; 4.35, s, CH_2.

Preparation of (139) using phosphorus pentachloride

Phosphorus pentachloride was added portionwise to methoxyacetic acid (10.0 g, 0.11 mol) with vigorous stirring until effervescence ceased. The mixture was stirred for 1 h at ambient temperature then fractionally distilled to give a colourless liquid, b.p. 110-114°, corresponding by ^1H n.m.r. and infrared spectroscopy to a mixture of (139) and phosphorus oxychloride. A second fractional distillation did not separate the components.

1-Methoxyhexan-2-one (141)

A solution of butylmagnesium bromide (0.17 mol) in anhydrous ether (220 ml) was slowly added to a rapidly stirred suspension of manganese(II) iodide[35] (53.40 g, 0.17 mol) in anhydrous ether (300 ml) at 0° under an

atmosphere of nitrogen. 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 methoxyacetyl chloride (15.00 g, 0.14 mol) in anhydrous ether (100 ml) was very slowly added and the resultant mixture was allowed to warm, with stirring, to ambient temperature overnight. The mixture was quenced with hydrochloric acid (5%) and the aqueous layer extracted twice with ether. The combined organic layers were washed with aqueous sodium thiosulphate solution (10%), saturated, aqueous sodium bicarbonate solution, dried and concentrated *in vacuo* The remaining solvent was removed by fractional distillation and the residue distilled to provide the *ketone* (141) (10.44 g, 57%) as a colourless liquid, b.p. 82-87°/32 mm (lit.[69] 95°/13 mm). ν_{max} (film) 1724 (C=O), 1116 cm^{-1} (C–O). ^1H n.m.r. δ 0.7-1.7, br, $CH_2CH_2CH_3$; 2.45, t, *J* 7 Hz, CH_2CO; 3.4, s, CH_3O; 3.8, s, CH_2O. Mass spectrum *m/z* 131 (M+1, 23%), 130 (M, 15), 85 (84), 57 (100).

Treatment of methoxyacetic acid with butyllithium

Butyllithium in hexane (2.0 M, 6.95 ml, 13.9 mmol) was added dropwise to a rapidly stirred solution of methoxyacetic acid (0.5 g, 5.55 mmol) in anhydrous tetrahydrofuran (50 ml) at 0° under a nitrogen atmosphere. The resulting mixture was stirred under nitrogen at ambient temperature overnight then introduced slowly, by cannula, to rapidly stirred hydrochloric acid (5%, 50 ml). The aqueous layer was extracted with ether (2 x 50 ml) and the combined organic layers dried and concentrated *in vacuo*. Solvent removal by

fractional distillation left a yellow oil (0.54 g), ν_{max} (film) 3436, 1734, 1458, 1198, 1126 cm^{-1}. ^1H n.m.r. δ 0.7-1.7, br; 2.4, m; 3.35, s; 3.4, s; 3.8, s; 4.0, s; 7.9, br.

1-Trimethylsilyl-3-methoxymethylhept-1-yn-3-ol (142)

Butyllithium in hexane (2.4 M, 19.7 ml, 47.3 mmol) was added dropwise to a stirred solution of trimethylsilylacetylene (5.07 g, 51.6 mmol) in anhydrous tetrahydrofuran (100 ml) at −70° under an atmosphere of nitrogen. The resulting mixture was stirred at −70° for 10 min. The ketone (141) (5.60 g, 43.0 mmol) in anhydrous tetrahydrofuran (40 ml) was added slowly at −70° and the resultant mixture stirred at this temperature for 20 min before being allowed to warm to room temperature. The mixture was quenched with saturated, aqueous ammonium chloride solution and the aqueous layer extracted twice with ether. The combined organic layers were dried and evaporated to give a yellow oil which was fractionally distilled under reduced pressure to provide the *alcohol* (142) (6.73 g, 69%) as a colourless liquid, b.p. 50-52°/0.01 mm Found: *m/z* 212.1604. $C_{12}H_{24}OSi$ (M−O) requires 212.1596. ν_{max} (CCl_4) 3576 (OH), 2956, 2824 (C–H), 2164 (C≡C), 1250, 1116 cm^{-1} (C–O). ^1H n.m.r. δ 0.15, s, $SiMe_2$; 0.7-1.6, br, $CH_2CH_2CH_2CH_3$; 2.3 (varies with sample concentration), s, OH; 3.3, s, CH_2O; 3.45, s, CH_3O. Mass spectrum *m/z* 228 (M, <1%), 212 (5), 183 (100), 171 (52).

3-Methoxymethylhept-1-yn-3-ol (143)

Tetrabutylammonium fluoride in tetrahydrofuran (1 M, 2 ml, 2 mmol) was added dropwise to a stirred solution of (142) (0.20 g, 0.88 mmol) in tetrahydrofuran (2 ml) at ambient temperature under an atmosphere of nitrogen and the resultant mixture stirred for 30 min. Volatiles were removed under reduced pressure and the residue extracted with ether (20 ml). The ethereal solution was washed with water (6 ml), hydrochloric acid (10%, 6 ml), water (6 ml), dried and evaporated to give a colourless oil which was flash chromatographed on silica gel. Elution with 18% ethyl acetate in hexane provided the *terminal alkyne* (143) (74 mg, 54%) as a colourless oil, b.p. 105°/25 mm (Found: C, 68.6; H, 9.9. $C_9H_{16}O_2$ requires C, 69.2; H, 10.3%). ν_{max} (film) 3444, 3304 (OH), 2952, 2864 (C–H), 2120 (w) (C≡CH), 1112 cm^{-1} (C–O). ^1H n.m.r. δ 0.7-1.6, br, $CH_2CH_2CH_2CH_3$; 2.2, s, C≡CH; 2.5 (varies with sample concentration), br, OH; 3.3, s, CH_2O; 3.4, s, CH_3O. Mass spectrum *m/z* 111 (M–CH_2OMe, 30%), 26 (100).

Preparation of (143) using ethynylmagnesium chloride

The ketone (141) (17.00 g, 0.13 mol) in anhydrous tetrahydrofuran (25 ml) was slowly added to an ice-cooled, stirred solution of ethynylmagnesium chloride[38] (0.18 mol) in anhydrous tetrahydrofuran (150ml) under an atmosphere of nitrogen and the resulting mixture allowed to warm to room temperature, at which it was stirred for 20 h. The reaction was quenched with saturated, aqueous ammonium chloride solution and the aqueous layer

extracted twice with ether. The combined organic layers were dried and evaporated to give a brown oil which was flash chromatographed on silica gel. Elution with 35% ether in hexane provided (143) (15.90 g, 78%) which was identical to that prepared earlier.

N-*[2-(3-Hydroxy-3-methylbut-1-ynyl)-4-methylphenyl]trifluoroacetamide (146)*

A stirred mixture of aryl bromide (14) (2.99 g, 10.6 mmol), alkynol (145) (1.34 g, 15.9 mmol), triphenylphosphine (40 mg), cuprous iodide (20 mg), triethylamine (8 ml), pyridine (5 ml) and *bis*(triphenylphosphine)palladium dichloride (20 mg) was heated at 85-90° for 22 h under an atmosphere of nitrogen. The mixture was cooled to room temperature, ethyl acetate (40 ml) added, the mixture stirred for 5 min then filtered. Ethylenediamine (2.5 ml) was added to the filtrate and the resultant mixture stirred at room temperature for 1 h then filtered. The filtrate was washed successively with water (25 ml), hydrochloric acid (10%, 2 x 25 ml), water (25 ml) and then dried and evaporated to give a brown oil which was flash chromatographed on silica gel. Elution with 20% ethyl acetate in hexane afforded the *alkynylbenzene* (146) (1.98 g, 65%) as a pale, yellow solid which was recrystallized from hexane to give pale, yellow crystals, m.p. 85.5-86° (Found: C, 59.0; H, 5.0. $C_{14}H_{14}F_3NO_2$ requires C, 59.0; H, 5.0%). ν_{max} (CCl_4) 3608 (OH), 3388 (NH), 2984 (C–H), 1744 (C=O), 1596, 1534 (Ar), 1288, 1152 (C–O). ^{1}H n.m.r. δ 1.6, s, $(CH_3)_2$; 2.3, s, $ArCH_3$; 2.4, s, OH; 7.1, dd, *J* 8, 2 Hz, ArH; 7.15, d, *J* 2 Hz, ArH; 8.1, d, *J* 8 Hz, ArH; 8.6, br, NH. Mass spectrum *m/z* 285 (M, 31%), 270 (18), 267 (21), 253 (16), 229 (65), 70 (100).

N-[2-(3-Hydroxy-3-methoxymethylhept-1-ynyl)-4-methylphenyl]trifluoro-acetamide (147)

A stirred mixture of aryl bromide (14) (0.35 g, 1.24 mmol), alkynol (143) (0.29 g, 1.86 mmol), triphenylphosphine (88 mg), cuprous iodide (44 mg), triethylamine (1 ml), pyridine (0.6 ml) and *bis*(triphenylphosphine)palladium dichloride (44 mg) was heated at 85-90° for 24 h under an atmosphere of nitrogen. The mixture was cooled to room temperature, ethyl acetate (5 ml) added, the mixture stirred for 15 min then filtered. Ethylenediamine (0.25 ml) was added to the filtrate and the resultant mixture stirred at room temperature for 3 h then filtered. The filtrate was washed successively with water (5 ml), hydrochloric acid (10%, 2 x 5 ml), water (5 ml), dried and evaporated to give a brown oil which was flash chromatographed on silica gel. Elution with 15% ethyl acetate in hexane provided the *alkynylbenzene* (147) (0.284 g, 64%) as a viscous, yellow oil, b.p. 120°/0.005 mm. (Found: C, 60.7; H, 6.3. $C_{18}H_{22}F_3NO_3$ requires C, 60.5; H, 6.2%). Found: *m/z* 357.1544. $C_{18}H_{22}F_3NO_3$ requires 357.1552. ν_{max} (CCl_4) 3576 (OH), 3380 (NH), 2932, 2860, 2828 (C–H), 1736 (C=O), 1596, 1532, (Ar), 1288, 1156 cm^{-1} (C–O). ^1H n.m.r. δ 0.7-1.7, br, $CH_2CH_2CH_2CH_3$; 2.35, s, $ArCH_3$; 2.75, s, OH; 3.35, d, *J* 9 Hz, CHOMe; 3.5, d, J 9 Hz, CHOMe; 7.15, dd, *J* 8, 2 Hz, ArH; 7.25, d, *J* 2 Hz, ArH; 8.3, d, *J* 8 Hz, ArH; 8.6, br, NH. Mass spectrum *m/z* 312 (M-CH_2OMe, 25%), 228 (6), 227 (6), 85 (100).

4-(2-Amino-5-methylphenyl)-2-methylbut-3-yn-2-ol (148)

A stirred mixture of aryl bromide (13) (1.15 g, 6.20 mmol), alkynol (145) (0.80 g, 9.30 mmol) triphenylphosphine (0.22 g), cuprous iodide (0.11 g), triethylamine (5 ml), pyridine (3 ml) and *bis*(triphenylphosphine)palladium dichloride (0.11 g) was heated at 85-90° for 14.5 h under an atmosphere of nitrogen. The mixture was cooled to room temperature, ethyl acetate (20 ml) added, the mixture stirred for 5 min then filtered. Ethylenediamine (0.65 ml) was added to the filtrate and the resultant mixture stirred at room temperature for 1 h then filtered. The filtrate was washed with water (2 x 20 ml), dried and evaporated to give a brown oil which was flash chromatographed on silica gel. Elution with 45% ethyl acetate in hexane afforded the *alkynylaniline* (148) (0.75 g, 64%) as a pale, yellow solid which was recrystallized from dichloromethane/hexane to provide off white prisms, m.p. 110-110.5° (Found: C, 76.2; H, 7.9. $C_{12}H_{15}NO$ requires C, 76.2; H, 8.0%). ν_{max} ($CDCl_3$) 3600 (OH), 3460, 3400 (NH_2), 2984, 2928 (C–H), 2240 (C≡C), 1620, 1600, 1504 (Ar), 1156 cm^{-1} (C–O). ^1H n.m.r. δ ($CDCl_3$) 1.65, s, $(CH_3)_2$; 2.2, s, $ArCH_3$; 3.6, br, NH, OH; 6.6, d, *J* 8 Hz, ArH; 6.95, dd, *J* 8, 2 Hz, ArH; 7.1, d, *J* 2 Hz, ArH. Mass spectrum *m/z* 189 (M, 100%), 171 (91), 132 (100).

1-(2-Amino-5-methylphenyl)-3-methoxymethylhept-1-yn-3-ol (149)

A stirred mixture of aryl bromide (13) (1.15 g, 6.20 mmol), alkynol (143) (1.45 g, 9.30 mmol), triphenylphosphine (0.22 g), cuprous iodide (0.11 g), triethylamine (5 ml), pyridine (3 ml) and *bis*(triphenylphosphine)palladium

dichloride (0.11g) was heated at 85-90° for 22 h under an atmosphere of nitrogen. The mixture was cooled to room temperature, ethyl acetate (20 ml) added, the mixture stirred for 5 min then filtered. Ethylenediamine (0.65 ml) was added to the filtrate and the resultant mixture stirred at room temperature for 1 h then filtered. The filtrate was washed with water (2 x 20 ml), dried and evaporated to give a brown oil which was flash chromatographed on silica gel. Elution with 40% ethyl acetate in hexane afforded the *alkynylaniline* (149) (0.89 g, 55%) as a pale yellow, viscous oil, b.p. 150°/0.005 mm. (Found: C, 73.9; H, 8.8. $C_{16}H_{23}NO_2$ requires C, 73.5; H, 8.9%). ν_{max} (CCl_4) 3580 (OH), 3492, 3392 (NH_2), 2928, 2862 (C–H), 2240 (C≡C), 1622, 1504 (Ar), 1152, 1116 (C–O). ^{1}H n.m.r. δ 0.7-1.7, br, $CH_2CH_2CH_2CH_3$; 2.2, s, $ArCH_3$; 3.2-3.8, m, $NH+CH_2O$; 3.45, s, CH_3O; 6.5, d, *J* 8 Hz, ArH; 6.85, dd, *J* 8, 2 Hz, ArH; 7.0, d, *J* 2 Hz, ArH. Mass spectrum *m/z* 261 (M, 20%), 216 (68), 158 (10), 144 (12), 132 (36), 85 (34), 57 (76), 28 (78), 18 (100).

Attempted synthesis of (150) using dicyclohexylborane

Cyclohexene (0.36 ml, 0.29 g, 3.50 mmol) was added dropwise to a stirred solution of borane-dimethylsulphide complex (1.75 mmol) in tetrahydrofuran (3 ml) at 0° under a nitrogen atmosphere. The resulting mixture was allowed to warm to 20°, stirred for 2 h, cooled to 0° then the alkyne (146) (0.20 g, 0.70 mmol) in tetrahydrofuran (1 ml) was added dropwise. The mixture was warmed to ambient temperature over 2 h and stirred at this temperature for a further 2 h. Acetic acid (0.7 ml) was added and the resulting solution was stirred for 11 h. The stirred solution was cooled to 0° then

basified by the dropwise addition of aqueous sodium hydroxide solution (5 M, 3 ml). Aqueous hydrogen peroxide (30%, 1 ml) was added dropwise and the resulting mixture stirred for 5 min. Water (8 ml) was added, followed by further stirring for 5 min. The aqueous layer was extracted twice with ether and the combined organic layers dried and evaporated to give the starting material (146).

Repetition of the reaction, except doubling the amount of borane, also resulted in the recovery of starting material.

N-*[2-(3-Hydroxy-3-methylbutyl)-4-methylphenyl]trifluoroacetamide (154)*

A mixture of alkynol (146) (100 mg, 0.35 mmol), Lindlar catalyst (5% palladium on calcium carbonate, poisoned with lead, 100 mg) and ethyl acetate (10 ml) was stirred under an atmosphere of hydrogen at ambient temperature for 30 min. The mixture was filtered through Celite and evaporated to afford the *title compound* (101 mg, 100%) as a white solid which was recrystallized from hexane to give white prisms, m.p. 89.5-90° (Found: C, 57.9; H, 6.2. $C_{14}H_{18}F_3NO_2$ requires C, 58.1; H, 6.3%). ν_{max} (CCl_4) 3620 (OH), 3504, 3272 (NH), 2972, 2928 (C–H), 1730 (C=O), 1606, 1536, 1502 (Ar), 1162 cm^{-1} (C–O). ^1H n.m.r. δ 1.2, s, $(CH_3)_2$; 1.7, t, *J* 7 Hz, CH_2; 1.95, s, OH; 2.3, s, $ArCH_3$; 2.65, t, *J* 7 Hz, CH_2; 6.9, d, *J* 2 Hz, ArH; 6.95, dd, *J* 8, 2 Hz, ArH; 7.65, d, J 8 Hz, ArH; 9.3, br, NH. Mass spectrum *m/z* 289 (M, 4%), 271 (8), 256 (4), 231 (2), 216 (10), 202 (3), 174 (7), 162 (16), 146 (22), 91 (24), 59 (100).

Repetition, except stopping the reaction after the uptake of 7.5 ml (approx. 1 molar equivalent) of hydrogen (4 min) resulted in isolation of (154) (21 mg, 21%) and (150) (57 mg, 57%) (see below for data) after flash chromatography on silica gel, eluting with 35% ether in hexane.

(Z)-N-[2-(3-Hydroxy-3-methylbut-1-enyl)-4-methylphenyl]trifluoroacetamide (150)

A mixture of (146) (1.50 g, 5.26 mmol), Lindlar catalyst (0.30 g), quinoline (0.30 g), biphenyl (0.15 g) and ethyl acetate (100 mmol) were stirred under an atmosphere of hydrogen at ambient temperature for 30 min (115 ml hydrogen uptake). The mixture was filtred through Celite, evaporated and the residue flash chromatographed on silica gel. Elution with 35% ether in hexane afforded the cis-*alkene* (150) (1.35 g, 90%) as a white solid which was recrystallized from hexane to give colourless crystals, m.p. 76.5-77°. Found *m/z* 287.1123. $C_{14}H_{16}F_3NO_2$ requires 287.1133. λ_{max} (EtOH) 207 nm. ν_{max} (CCl_4) 3604 (OH), 3408 (NH), 2976, 2928 (C–H), 1732 (C=O), 1596, 1530 (Ar), 1284, 1162 cm^{-1} (C–O). ^1H n.m.r. δ ($CDCl_3$, 300 MHz) 1.30, s, $(CH_3)_2$; 1.76, s, OH; 2.33, s, $ArCH_3$; 5.94, d, *J* 12.3 Hz, C=C–H; 6.27, d, *J* 12.3 Hz, C=C–H; 6.99, s, ArH; 7.11, d, *J* 8.4 Hz, ArH; 7.72, d, *J* 8.4 Hz, ArH; 9.02, br, NH. Mass spectrum *m/z* 287 (M, 23%), 272 (18), 269 (17), 254 (68), 230 (37), 43 (100).

(Z)-4-(2-Amino-5-methylphenyl)-2-methylbut-3-en-2-ol (151)

A mixture of the trifluoroacetamide (150) (0.633 g, 2.20 mmol) and methanolic potassium hydroxide (10%, 25 ml) was heated under reflux for 2.5 h. Water (60 ml) was added and the resultant mixture was extracted four times with dichloromethane. The combined organic layers were dried and evaporated to give a pale yellow oil which was flash chromatographed on silica gel. Elution with 50% ethyl acetate in hexane yielded the *amine* (151) (0.40 g, 95%) as an off-white solid which was recrystallized from hexane m.p. 46-47°. Found: *m/z* 191.1302. $C_{12}H_{17}NO$ requires 191.1310. ν_{max} (CCl_4) 3580 (OH), 3440, 3396 (NH_2), 2976, 2928 (C–H), 1622, 1504 cm^{-1} (Ar). ^1H n.m.r. δ 1.25, s, $(CH_3)_2$; 2.2, s, $ArCH_3$; 3.3, br, NH_2+OH; 5.75, d, *J* 12 Hz, C=C–H; 6.15, d, *J* 12 Hz, C=C–H; 6.45, d, *J* 8 Hz, ArH; 6.75, s, ArH; 6.8, d, *J* 8 Hz, ArH. Mass spectrum *m/z* 191 (M, 31%), 158 (100).

Attempted cyclization of (151) (hydrochloric acid/copper)

A mixture of the aminoalcohol (151) (6 mg, 0.50 mmol), calcium chloride (26 mg, 0.25 mmol), cuprous chloride (21 mg, 0.20 mmol), copper/bronze powder (*ca* 3 mg) was stirred at ambient temperature for 5 h. The mixture was basified with aqueous sodium hydroxide solution (5 M) and extracted twice with ether. The combined organic layers were dried and evaporated to give a brown intractable mixture (*ca* 55 mg).

Attempted cyclization of (150) (hydrochloric acid/copper)

A mixture of amidoalcohol (150) (0.146 g, 0.50 mmol), calcium chloride (26 mg, 0.25 mmol), cuprous chloride (21 mg, 0.20 mmol), copper/bronze powder (*ca* 3mg) and concentrated hydrochloric acid (3 ml) was stirred at ambient temperature for 3 h. Ether (20 ml) was added and the mixture stirred for 5 min. The organic layer was washed with concentrated hydrochloric acid (2 x 5 ml), water (2 x 5 ml), dried (K_2CO_3) and evaporated to give a brown, intractable mixture (*ca* 0.11 g).

Attempted cyclization of (150) (hydrochloric acid/copper-two phase)

A mixture of amidoalcohol (150) (73 mg, 0.25 mmol), calcium chloride (13 mg, 0.13 mmol), cuprous chloride (11 mg, 0.10 mmol), copper/bronze powder (*ca* 2 mg), concentrated hydrochloric acid (1.5 ml) and dichloromethane (1.5 ml) was stirred rapidly at ambient temperature for 45 min. Dichloromethane (10 ml) was added, the mixture shaken and the organic layer washed with concentrated hydrochloric acid (3 ml), water (3 ml), saturated, aqueous sodium bicarbonate solution (3 ml), water (3 ml), dried and evaporated. The residue was flash chromatographed on silica gel. Elution with 20% ether in hexane yielded three fractions, two of which were complex mixtures according to t.l.c. and ^{1}H n.m.r. spectroscopic data. The other fraction (highest R_F) was a white solid (15 mg) whose spectral characteristics are compatible with the *diene* (155), λ_{max} (EtOH) 280 nm. ν_{max} ($CDCl_3$) 3420, 1730, 1536, 1162 cm^{-1}. ^{1}H n.m.r. δ ($CDCl_3$, 300 M Hz) 1.96, s,

3H; 2.36, s, 3H; 5.17, s, 2H; 6.45, d, *J* 16.0 Hz, 1H; 6.78, d, *J* 16.0 Hz, 1H; 7.12, d, *J* 8.1 Hz, 1H; 7.31, s, 1H; 7.63, d, *J* 8.1 Hz, 1H; 7.84, br, 1H. Mass spectrum *m/z* 269 (46%), 254 (60), 156 (100).

Attempted cyclization of (150) (methanesulphonic acid)

A mixture of (150) (75 mg, 0.26 mmol), methanesulphonic acid (0.16 g, 1.68 mmol) and dichloromethane (4 ml) was stirred at ambient temperature under an atmosphere of nitrogen for 1 h. More dichloromethane (20 ml) was added and the mixture washed with water (10 ml), dried and evaporated to yield an intractable mixture (*ca* 70 mg).

An analogous reaction using benzene as solvent returned an intractable mixture, as did a third reaction in dichloromethane which was carried out at −10° for 20 min.

Attempted cyclization of (151) (acetic acid)

A mixture of the amine (151) (60 mg, 0.31 mmol) and acetic acid (3 ml) was heated under reflux for 24 h. The mixture was diluted with ether and basified with saturated, aqueous sodium becarbonate solution. The aqueous layer was extracted twice with ether and the combined organic layers were dried and evaporated to afford a viscous, brown, intractable oil (*ca* 40 mg).

Attempted cyclization of (151) (hexafluoroisopropanol/para-toluene-sulphonic acid)

A mixture of (151) (55 mg, 0.29 mmol) and 1,1,1,3,3,3-hexafluoropropan-2-ol (2.5 ml) was heated at reflux under nitrogen for 21 h. *para*-Toluenesulphonic acid (*ca* 4 mg) was added and the mixture heated under reflux for a further 4 h. The mixture was diluted with dichloromethane and basified with saturated, aqueous sodium bicarbonate solution. The aqueous layer was extracted twice with dichloromethane and the combined organic layers dried and evaporated to give a viscous, yellow oil which was flash chromatographed on silica gel. Elution with 40% ether in hexane provided one major fraction which had a poorly resolved ^{1}H n.m.r. spectrum and complex infrared and mass spectra, perhaps indicating a polymeric mixture.

Attempted cyclization of (151) (palladium acetate)

A stirred mixture of (151) (50 mg, 0.26 mmol), palladium acetate trimer (20 mg), triphenylphosphine (23 mg) and acetonitrile (3ml) was heated at reflux under a nitrogen atmosphere for 2 h. Ethyl acetate (10 ml) was added and the mixture stirred for 5 min, filtered, washed with brine, dried and evaporated to give a brown oil which was flash chromatographed on silica gel. Elution with 70% ethyl acetate in hexane provided a major fraction (23 mg) which contained, by ^{1}H n.m.r. and infrared spectroscopy and mass spectrometry, a complex mixture of products.

Treatment of aminoalcohol (151) with acetyl chloride/pyridine

(a) Acetyl chloride (44 µl, 49 mg; 0.62 mmol) was added dropwise to a stirred solution of (151) (40 mg, 0.21 mmol) in pyridine (1 ml) at 0° under a nitrogen atmosphere. The resulting mixture was allowed to warm to ambient temperature, stirred for 22 h and evaporated under reduced pressure. The residue was dissolved in dichloromethane and washed with hydrochloric acid (5%). The aqueous layer was extracted twice with ether, dried and evaporated to give a viscous, brown, intractable oil.

(b) Acetyl chloride (50 µl, 54 mg, 0.69 mmol) was added dropwise to a stirred solution of (151) (40 mg, 0.21 mmol) in pyridine (1 ml) at 0° under an atmosphere of nitrogen. The resulting mixture was stirred at 0° under nitrogen for 90 min and then evaporated under reduced pressure. The residue was partitioned between ether and water, shaken and the organic layer dried and evaporated. The residue was flash chromatographed on silica gel. Elution with 75% ethyl acetate in hexane provided two main fractions;- (a) a white solid (14 mg), tentatively assigned the diene structure (160) Found: *m/z* 215.1301. $C_{14}H_{17}NO$ requires 215.1310. ν_{max} ($CDCl_3$) 3436, 2980, 2240, 1682, 1590, 1512 cm^{-1}. ^1H n.m.r. δ ($CDCl_3$) 1.95, s, 3H; 2.2, s, 3H; 2.35, s, 3H; 5.1, s, 2H; 6.45-6.9, m, >2H; 6.9-7.8, m, >4H. Mass spectrum *m/z* 215 (26%), 200 (29), 172 (55), 158 (100) and (b) a white solid (14 mg), tentatively assigned the amide structure (159). Found: *m/z* 233.1457. $C_{14}H_{19}NO_2$ requires 233.1416. ν_{max} ($CDCl_3$) 3620, 3428, 2976, 2240, 1682, 1590, 1516 cm^{-1}. ^1H n.m.r δ ($CDCl_3$) 1.3, s, 6H; 1.95, br, 1H; 2.15, s, 3H; 2.35,s, 3H; 5.9, d, *J* 12 Hz, 1H; 6.3, d, *J* 12 Hz, 1H; 6.95, s, 1H; 7.05, d, *J* 8 Hz, 1H; 7.6, br, 1H; 7.75, d, *J* 8 Hz, 1H. Mass spectrum *m/z* 233 (49%), 215 (14), 190 (21), 158 (100).

Treatment of amidoalcohol (150) with acetyl chloride/pyridine

Acetyl chloride (92 µl, 100 mg, 1.29 mmol) was added dropwise to a stirred solution of (150) (74 mg, 0.26 mmol) in pyridine (1.5 ml) at 0° under an atmosphere of nitrogen. The resulting mixture was stirred at 0° for 3 h, at room temperature for 21 h and then cooled to 0°. Acetyl chloride (60 ml) was added, the mixture stirred at ambient temperature for a further 17 h then evaporated under reduced pressure. The residue was partitioned between ether and water, shaken and the organic layer dried and evaporated to give an intractable mixture (*ca* 70 mg).

CHAPTER 4

3-Chloro-3-methylbut-1-yne (169)

Prepared by the procedure of Cooper[19], ^{1}H n.m.r.[19], b.p. 73-75° (lit.[19] 73-76°). ν_{max} (film) 3300 (≡C–H), 2984 (C–H), 2140 (C=C), 780 cm^{-1} (CCl). ^{1}H n.m.r. δ 1.85, s, $(CH_3)_2$; 2.5, s, C≡C–H.

N-*(1,1-Dimethylpropynyl)aniline (172)*

Prepared by the procedure of Cooper[19] to give a product identical to authentic material, ^{1}H n.m.r. δ 1.6, s, $(CH_3)_2$; 2.2, s, C≡C–H; 3.4, br, NH; 6.7-7.3, m, ArH. Mass spectrum *m/z* 159 (M, 75%), 144 (100).

3-Chloro-3-methoxymethyl-1-trimethylsilylhept-1-yne (170)

The alcohol (142) (12.00 g, 52.2 mmol) was added slowly to a stirred mixture of calcium chloride (2.66 g, 26.1 mmol), cuprous chloride (2.14 g, 21.4 mmol), copper/bronze powder (0.24 g) and concentrated hydrochloric acid (235 ml) at room temperature. The resulting mixture was stirred at ambient temperature for 50 h then extracted with dichloromethane (3 x 200 ml). The combined organic layers were washed with concentrated hydrochloric acid (2 x 100 ml),

water (3 x 100 ml), dried and evaporated to yield a yellow oil which was fractionally distilled under reduced pressure to give the *chloride* (170) (8.77 g, 68%) as a colourless liquid, b.p. 52-54°/0.07 mm (Found: C, 58.1; H, 9.3. $C_{12}H_{23}ClOSi$ requires C, 58.4; H, 9.4%). ν_{max} (film) 2956 (C–H), 2168 (C≡C), 1252 (C–O), 844, 760 cm^{-1} (CCl). ^1H n.m.r. δ 0.2, s, $SiMe_3$; 0.8-2.0, br, $CH_2CH_2CH_2CH_3$; 3.45, s, CH_3O; 3.55, s,CH_2O. Mass spectrum *m/z* 231 (<1)/233 (M-15, <1%), 211 (2) 210 (2), 201 (1), 195 (2), 181 (3), 165 (3), 100 (100).

N-*(1-Butyl-1-methoxymethylprop-2-ynyl)aniline (173)*

A stirred mixture of aniline (0.102 g, 1.08 mmol), chloride (170) (0.222 g, 0.90 mmol), triethylamine (0.20 ml, 0.146 g, 1.44 mmol), cuprous chloride (6 mg), copper/bronze powder (6 mg), tetrahydrofuran (4 ml) and water (1 ml) was heated under reflux for 14 h. Water (4 ml) was added and the mixture extracted three times with ether. The combined organic layers were dried and evaporated and the residue flash chromatographed on silica gel. Elution with 15% ethyl acetate in hexane provided the *title compound* (0.108 g, 52%) as a pale yellow, viscous oil, b.p. 75°/0.02 mm (Found: C, 78.1; H, 9.2. $C_{15}H_{21}NO$ requires C, 77.9; H, 9.2%). ν_{max} (film) 3396 (NH), 3296 (≡C–H), 3052, 2952, 2928, 2864, (C–H), 1602, 1504 (Ar), 1108 (C–O), 750, 696 cm^{-1} (Ar–H). ^1H n.m.r. δ 0.75-2.1, br, $CH_2CH_2CH_2CH_3$; 2.3, s, C≡CH; 3.35, s, CH_3O; 3.5, s, CH_2O; 3.75, br, NH; 6.6-7.25, m, ArH. Mass spectrum *m/z*/ 231 (M, 14%), 186 (100), 174 (39), 156 (50).

An analogous reaction carried out at ambient temperature for 4 days, resulted in formation of (173) in 54% yield.

N-*(1,1-Dimethylpropynyl)-2-bromo-4-methylaniline (174))*

Prepared by the procedure of March[48], b.p. 80°/0.5 mm (lit.[48] 80°/0.5 mm). ^{1}H n.m.r. δ (CCl_4, 300 MHz) 1.61, s, $(CH_3)_2$; 2.21, s, $ArCH_3$; 2.23, s, C≡CH; 4.11, br, NH; 6.88, dd, *J* 8.3, 1.4 Hz, ArH; 7.15, d, *J* 8.3 Hz, ArH; 7.18, d, *J* 1.4 Hz, ArH. ^{13}C n.m.r. δ ($CDCl_3$, 75.47 MHz) 20.00, $ArCH_3$; 30.31, $(CH_3)_2$; 49.83, C–N; 71.72, C≡C–H; 86.42, C≡C–H; 112.68, C-2; 117.13, C-6; 128.35, C-5; 128.46, C-4; 132.72, C-3; 140.22, C-1. Mass spectrum *m*/z251/253 (M, 57%), 236/238 (87), 185/187 (100).

N-*(1-Butyl-1-methoxymethylpropynyl)-2-bromo-4-methylaniline (175)*

A stirred mixture of aniline (13) (0.68 g, 3.67 mmol), chloride (170) (0.75 g, 3.06 mmol), triethylamine (0.68 ml, 0.50 g, 4.90 mmol) cuprous chloride (20 mg), copper/bronze powder (20 mg), tetrahydrofuran (14 ml) and water (3.5 ml) was heated under reflux for 6 h. Water (14 ml) was added and the mixture extracted three times with ether. The combined organic layers were dried and evaporated and the residue flash chromatographed on silica gel. Elution with 5% ether in hexane provided the *title compound* (0.221 g, 22%) as a pale, yellow, viscous oil, b.p. 100°/0.005 mm (Found: C, 59.4; H, 6.7.

$C_{16}H_{22}BrNO$ requires C, 59.3; H, 6.8%). ν_{max} (film) 3400 (NH), 3296 (≡C–H), 2950, 2924, 2864 (C–H), 1612, 1514, (Ar), 1108 (C–O), 810 cm^{-1}. ^1H n.m.r. δ 0.7-2.0, br, $CH_2CH_2CH_2CH_3$; 2.2, s, $ArCH_3$; 2.3, s, C≡CH; 3.35, s, CH_3O; 4.45, br, NH; 6.85 dd, *J* 8, 2 Hz, ArH; 7.15, d, *J* 2 Hz, ArH; 7.25, d, *J* 8 Hz, ArH. Mass spectrum *m/z* 323/325 (M, 8%), 278/280 (100). Further elution with 25% ether in hexane afforded the starting aniline (13) (0.433 g, 64%).

Increased reaction times did not improve the yield of coupled amine (175).

Reaction of aminoester (134) with chloride (169)

A mixture of aminoester (134) (0.22 g, 0.9 mmol), chloride (169) (0.092 g, 0.90 mmol), triethylamine (0.125 g, 0.17 ml, 1.20 mmol), cuprous chloride (3 mg), copper/bronze powder (3 mg), ether (3.5 ml) and water (1 ml) was stirred at ambient temperature for 30 h. Water was added and the mixture extracted twice with dichloromethane. The combined organic layers were dried and evaporated and the residue flash chromatographed on silica gel. Elution with 5% ether in hexane provided an impure, off white solid (45 mg) whose spectral characteristics were compatible with the N-*substituted amine* (176). Found: *m/z* 309.0375. $C_{14}H_{16}BrNO_2$ requires 309.0364. ν_{max} (CCl_4) 3408, 3304, 2980, 1712, 1600, 1518, 1272, 1248, 1110 cm^{-1}. ^1H n.m.r. δ 1.35, t, *J* 7 Hz, 3H; 1.7, s, 6H; 2.3, s, 1H; 4.25, q, *J* 7 Hz, 2H; 4.7, br, 1H; 7.2, d, *J* 8 Hz, 1H; 7.8, dd, *J* 8, 2 Hz, 1H; 8.0, d, *J* 2 Hz, 1H. Mass spectrum *m/z* 309/311 (51%), 294/296 (100). Further elution afforded the starting aminoester (134) (0.167 g).

Repetition of the reaction, except using refluxing tetrahydrofuran instead of ether, provided a similar result.

Attempted radical cyclization of (175)

A solution of the *N*-propargylaniline (175) (50 mg, 0.15 mmol), tributylstannane (90 µl, 0.32 mmol) and azobisisobutyronitrile (catalytic, *ca* 3 mg) in benzene (6 ml) was heated at reflux under an atmosphere of nitrogen, with addition of azobisisobutyronitrile (3 mg) every 20 h, for a total of 95 h. The benzene was removed under reduced pressure, ether (3 ml) and saturated, aqueous potassium fluoride solution (5 ml) were added and the resultant mixture stirred for 6 h. Ether (25 ml) was added, the mixture shaken and the organic layer washed with water (5 ml), brine (5 ml) dried and evaporated. The residue was flash chromatographed on silica gel. Elution with 2% ether in hexane afforded the starting material (175).

(E)-N-*(2,3-Dibromo-1,1-dimethylprop-2-enyl)*-2-bromo-4-methylaniline *(180)*

Prepared by the procedure of March[48] to give a product identical to authentic material. ^{1}H n.m.r. δ ($CDCl_3$, 300 MHz) 1.74, s, $(CH_3)_2$; 2.22, s, $ArCH_3$; 4.72, br, NH; 6.57, d, *J* 8.3 Hz, ArH; 6.64, s, BrC=CHBr; 6.95, dd, *J* 8.3, 1.7 Hz, ArH; 7.28, d, *J* 1.7 Hz, ArH. Mass spectrum *m/z* 409 (M, 36%)/411 (95)/413 (100)/415 (38), 394 (18)/396 (49)/398 (58)/400 (18), 378 (8)/380 (25)/382 (25)/384 (8).

Attempted synthesis of dihydroquinoline (181)

(a) A stirred mixture of the bromoamine (180) (73 mg, 0.18 mmol), hexabutyldistannane (116 mg, 0.20 mmol), *tetrakis*(triphenylphosphine) palladium (0) (20 mg), 2,6-di*tert*-butyl-4-methylphenol (*ca* 2 mg) and 1,4-dioxane (1 ml) was heated at reflux under an atmosphere of nitrogen for 25 h. The mixture was cooled to ambient temperature, aqueous potassium fluoride solution (20%, 3 ml) added and the resulting mixture stirred rapidly for 3.5 h. Ether (10 ml) was added, the mixture shaken and the aqueous layer extracted with ether. The combined organic layers were washed with brine, dried and evaporated to give a brown oil (136 mg) corresponding by t.l.c. and ^{1}H n.m.r. spectroscopy to a mixture of tributylstannanes and starting material (180).

(b) A stirred mixture of the bromoamine (180) (82 mg, 0.20 mmol), hexamethyldistannane (73 mg, 0.22 mmol), *tetrakis*(triphenylphosphine) palladium (0) (20 mg), 2,6-di*tert*-butyl-4-methylphenol (*ca* 2 mg) and 1,4-dioxane (2 ml) was heated at reflux under a nitrogen atmosphere for 20 h. The mixture was washed with aqueous ammonium hydroxide solution (10%) and the organic layer filtered through Celite. The filtrate was washed with brine, dried and evaporated to give a brown oil which was flash chromatographed on silica gel. Elution with 0.25% ether in hexane afforded two main fractions:- (a) a yellow oil (4 mg), corresponding by t.l.c. and ^{1}H n.m.r. spectroscopy to unreacted dibromoalkene (180) and (b) a yellow oil (5 mg), corresponding by t.l.c., ^{1}H and ^{13}C n.m.r. spectroscopy and mass spectrometry to the *N*-propargylaniline (174). Further elution with an

increased proportion of ether afforded a third fraction as a yellow oil (11 mg), corresponding by t.l.c. and ^1H n.m.r. spectroscopy to the aniline (13).

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