The Synthesis of Tetrahydroquinolines Related to Virantmycin

Craig L. Francis, Natalie M. Williamson, A. David Ward*

Department of Chemistry, University of Adelaide, Adelaide, S.A. 5005, Australia
Fax +61(8)83034358; E-mail: david.ward@adelaide.edu.au

Received 21 June 2004

Abstract: 4-Substituted anilines react with 1-methoxymethyl-1-butyl-3-trimethysilylpropargyl chloride but not with 1,1-dibutyl-3-trimethylsilylpropargyl chloride, to form the corresponding substituted *N*-propargylanilines. These anilines cyclise, using cuprous chloride, in the presence of trifluoroacetic anhydride, and, when the aniline substituent is electron donating, to give 6-substituted 2-butyl-2-methoxymethyl-1-trifluoroacetyl-1,2-dihydroquinolines. Chlorination, followed by selective dechlorination using sodium cyanoborohydride, of the 6-methyl product yields 2-butyl-2-methoxymethyl-3-chloro-6-methyl-1-trifluoroacetyl-1,2,3,4-tetrahydroquinoline which has the same relative stereochemistry as that in the antiviral compound, Virantmycin.

Key words: quinolines, diastereoselectivity, cyclisations, alkyl halides, alkynes, antiviral agents

For some time we have been interested[1] in synthetic approaches to analogues of the antiviral compound Virantmycin[2] (**1**) (Figure 1) with a view to establishing viable routes to a range of compounds that would ultimately provide information on the structural factors necessary for antiviral activity.

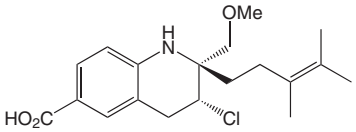

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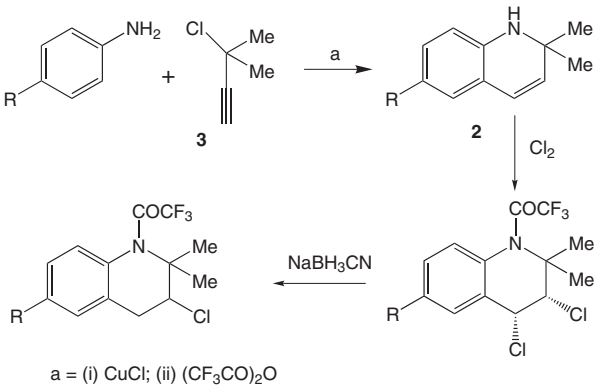
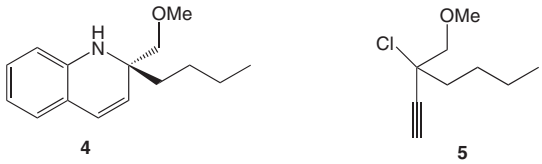
Figure 1

We have recently described[1f] the preparation and some chemistry (Scheme 1) of 2,2-dimethyl-1,2-dihydroquinolines **2**, and it was of interest to establish whether our results from this study could be applied to similar systems containing larger side chains, more related to those present in Virantmycin, at the 2 position of the dihydroquinoline. We have already noted[3] that the size of the side chains at the carbon to which the chlorine is attached in the chloroacetylene **3** is an important factor in determining whether these systems will react with anilines, to the extent that large groups at this position can prevent the reaction from occurring. We chose to investigate a system **4** (Figure 2) with methoxymethyl and butyl side chains at the 2 position, as these groups closely resemble those present in Virantmycin, particularly in terms of size, with the added advantage that the butyl side chain does not contain any functional group whose presence may complicate the use of the chemistry that we have established[1f] with the 2,2-dimethyl-substituted quinoline systems.



Scheme 1

The synthesis of the chloroacetylene **5**, needed to prepare these 2-methoxymethyl-2-butyl-1,2-dihydroquinolines was initially approached as outlined in Scheme 2. Methoxyacetic acid was converted to the corresponding acid chloride, which was reacted with butylmanganese iodide,[4] prepared from butylmagnesium bromide and manganese(II) iodide, to give the ketone **6** in variable yield, with the best being 57%. A more direct approach[5] using butyllithium (2.2 equiv) and methoxyacetic acid was less successful as it gave a mixture of the ketone **6** and the carbinol **7**.

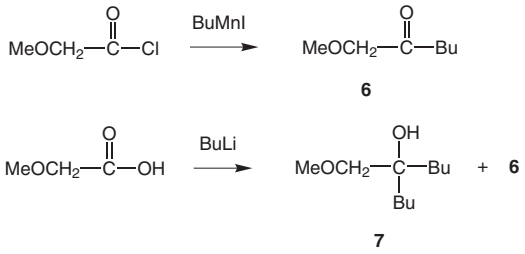


4 **5**

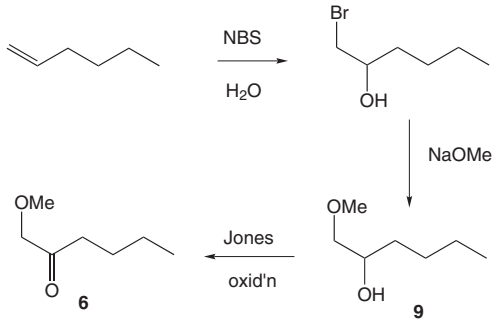
Figure 2

Because of the variability in the yield of these reactions using organometallic reagents we turned our attention to an alternative approach (Scheme 3). 1-Hexene was converted in excellent yield to the bromohydrin **8**, which reacted readily with sodium methoxide to give the hydroxy ether **9**, which was smoothly oxidised, using Jones reagent, to the desired ketone **6**. The ketone **6** reacted with either ethynylmagnesium chloride to give the acetylene

SYNTHESIS 2004, No. 16, pp 2685–2691
Advanced online publication: 22.09.2004
DOI: 10.1055/s-2004-831234; Art ID: P06304SS

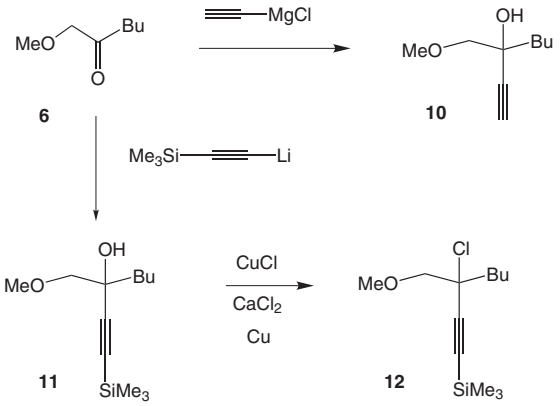


Scheme 2



Scheme 3

10, or with the lithium salt of trimethylsilylacetylene to give the acetylenic alcohol **11** (Scheme 4). It became apparent from later reactions that it was advantageous to retain the trimethylsilyl protecting group and remove it at a later stage, using tetrabutylammonium fluoride if necessary, so our general approach was to use the trimethylsilylacetylene system. The acetylenic alcohol **11** was readily converted to the corresponding acetylenic chloride **12** using a mixture of cuprous chloride, calcium chloride and copper bronze in concentrated hydrochloric acid (Scheme 4).[5]



Scheme 4

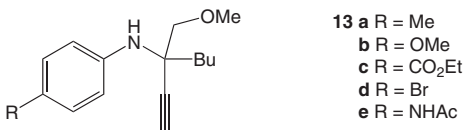


Figure 3

The acetylenic chloride **12** reacted with a range of *p*-substituted anilines to give the substituted amines **13a–e** (Figure 3), using the same conditions we have previously established[5] for the acetylenic chloride **3** (Scheme 1); however, the reaction times were considerably slower (24 h for the reaction of **12** with *p*-toluidine compared with 1 h for the reaction of **3** with the same aniline). Attempting the reactions at higher temperatures resulted in extensive decomposition. The reaction of ethyl 4-aminobenzoate with the chloride **12** was incomplete even after 72 h and the coupled product **13c** was obtained in only 41% yield. However the reaction of **12** with *p*-anisidine was complete after 2.5 h, as indicated by TLC, although the coupled product **13e** was only obtained in 38% yield. During the course of these reactions, or their workup, the trimethylsilyl group is removed and the products are monosubstituted acetylenes.

To evaluate further the effect of increasing size of substituents attached to the α-carbon of the acetylene on this coupling reaction, we prepared the dibutyl system **14** (Figure 4) (from 5-nonanone, using the chemistry shown in Scheme 4). This acetylenic chloride did not react at all with *p*-toluidine and the starting materials were largely recovered after 24 h. These results indicate that the coupling reaction is significantly affected by steric factors, and also the nature of the 4-substituent of the aniline, with electron donating groups facilitating the coupling and electron withdrawing groups retarding it.

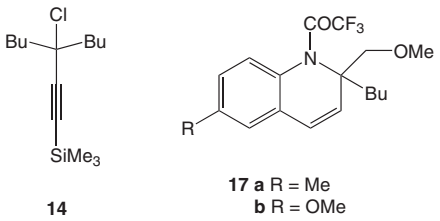
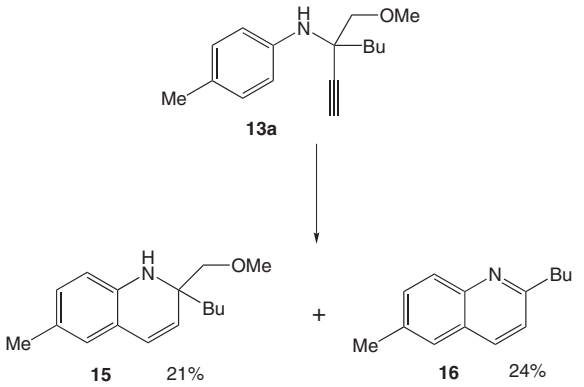


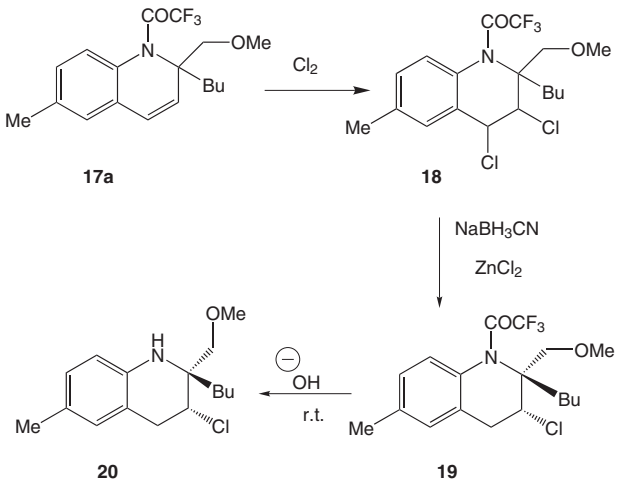
Figure 4

The cyclisation of the substituted amine **13a** occurred using the same conditions that had previously been used[1f] for the dimethyl substituted systems (Scheme 1). However, the dihydroquinoline **15** was obtained in only 21% yield. Also isolated was the quinoline **16** in 24% yield (Scheme 5). The dihydroquinoline **15** converts to the quinoline system **16** (presumably by elimination of dimethyl ether) on standing. For this reason the cyclisation of these methoxymethyl substituted systems **13a–e** were attempted using our standard conditions,[1f] but trifluoroacetic anhydride was added to the reaction mixture after the reaction had cooled and before workup. In this manner the dihydroquinolines **17a**,**b** were obtained. However, the products from the attempted cyclisations of **13c–e** were complex mixtures whose NMR spectra did not show any of the expected signals for the dihydroquinoline products (particularly the alkene hydrogen signals). The ester **13c** was substantially recovered from a reaction using the standard cyclisation conditions without the addition of tri-

fluoroacetic anhydride. Thus it appears that the presence of electron withdrawing groups at the 4-position of the aniline ring inhibits the cyclisation when the substituents at the 3-position of the acetylenic chloride are larger than methyl groups.



Scheme 5



Scheme 6

The *N*-trifluoroacetyldihydroquinoline **17a** was successfully chlorinated[1f] to give the *cis*-dichlorotetrahydroquinoline **18** ($J_{3,4}$ = 6.2 Hz) which was selectively dechlorinated[1f] to give the monochloride **19** in excellent yield (Scheme 6). The ^{1}H NMR spectrum of **19** showed the three sets of doublet-of-doublets expected for the CH_2CHCl ABX system at δ = 3.06 (benzylic hydrogen, J = 4.3, 16.0 Hz), 3.53 (benzylic hydrogen, J = 7.2, 16.0 Hz) and 4.28 (CHCl, J = 4.3, 7.2 Hz). Irradiation at δ = 4.28 resulted in an NOE enhancement of the adjacent benzylic methylene hydrogen only. Irradiation of one of the doublets of the OCH_2 AB quartet at δ = 3.90 gave enhancement of the signal for the other part of the quartet only. However, irradiation at δ = 1.9 (the methylene group closest to the nitrogen atom in the butyl chain) gave a 1.7% enhancement of the OCH_2 AB doublet-of-doublets and a 1.4% enhancement of the hydrogen attached to the chlorine-bearing carbon atom. The latter enhancement suggests that the butyl group and the methine hydrogen atom are in a *cis* arrangement on the heterocyclic ring, which in turn suggests the stereochemistry shown in **19**. It is possible that the stereoselectivity observed in **19** was introduced during chlorination of the dihydroquinoline **18**. Complexation of chlorine by the oxygen of the methoxyl group could facilitate polarisation of the chlorine molecule as well as favouring delivery from the face corresponding to the side of the double bond that the methoxyl group is on. It is possible that the participation of the trifluoroacetyl group, leading[1f] to the *cis* dichlorides formed in simpler systems, may also be a factor controlling the observed stereochemistry.

Tetrahydroquinoline *N*-trifluoroacetamides are usually hydrolysed relatively easily under basic conditions,[1c,e] but it was anticipated that this type of hydrolysis may pose a problem with the 3-chloro systems, since the basic conditions could facilitate elimination, and/or the anion on nitrogen formed under these conditions could intramolecularly displace chlorine to form an aziridine system. This type of aziridine formation has been observed for similar systems,[1c,2d] and attempts to selectively ring open the aziridine system resulted in mixtures of tetrahydroquinolines and unwanted dihydroindoles.[1c] The trifluoroacetamide **19** was unaffected by acidic hydrolysis conditions and, as expected, basic hydrolysis under reflux conditions gave a complex mixture of products. However, stirring the trifluoroacetamide **19** with potassium hydroxide in methanol at room temperature provided the parent amine **20** in good yield (Scheme 6).

Our results show that the chemistry described above provides a convenient methodology for the preparation of a range of 2,2,3,4-, and 2,2,3-substituted tetrahydroquinolines that are closely related to Virantmycin. They also provide indications of the limitations of some of the key reactions. Taken together with our previous results they provide good leads for the synthesis of Virantmycin analogues with a range of substituents at the 2, 3 and 4 positions of the heterocyclic ring, as well as a variety of substituents on the aromatic ring.

Melting points were recorded on a Kofler hot stage apparatus equipped with a Reichert microscope and are uncorrected. Microanalyses were performed by the Canadian Microanalytical Service, Vancouver; Chemical and Microanalytical Services, Melbourne, or the Chemistry Department, University of Otago. Flash chromatography refers to nitrogen-pressure driven rapid chromatography using Merck silica gel, pore diameter 60 Å. Light petroleum refers to the fraction with bp 66–68 °C. IR spectra were recorded on a Jasco A102 or a Jasco IRA-1 grating spectrometer. ^{1}H NMR spectra were recorded on a Bruker ACP300 spectrometer operating at 300 MHz in deuterochloroform solution, with tetramethylsilane as an internal standard. Electron impact MS were recorded at 70 eV on an AEI MS3074 or a VG ZAB 2HF spectrometer. Accurate mass measurements (HRMS) were made either on an AEI MS3074 spectrometer or by the Chemistry Department, University of Melbourne using a JEOL AX505H spectrometer.

Methoxyacetyl Chloride

Methoxyacetic acid (15 g, 170 mmol) and thionyl chloride (29.76 g, 250 mmol) were refluxed at 110–120 °C under an atmosphere of ni-

trogen for 2 h. The mixture was fractionally distilled through a 20 cm Vigreux column.

Yield: 11.40 g (63%); colourless liquid; bp 109–113 °C (lit.[6] 105–110 °C).

IR (film): 1800, 1200, 1130, 750 cm^{-1}.

^1H NMR: δ = 3.50 (s, 3 H, OMe), 4.38 (s, 2 H, OCH_2).

1-Methoxyhexan-2-one (6)

(a) A solution of butylmagnesium bromide (0.17 mol) in anhyd Et_2O (220 mL) was slowly added to a rapidly stirred suspension of manganese(II) iodide (53.40 g, 0.17 mol) in anhyd Et_2O (300 mL) at 0 °C under an atmosphere of anhyd nitrogen. The resulting mixture was stirred at 0–5 °C for 10 min then at r.t. for 30 min. After cooling to –60 °C, a solution of methoxyacetyl chloride (15.00 g, 0.14 mol) in anhyd Et_2O (100 mL) was added very slowly and the resultant mixture was allowed to warm, with stirring, to r.t. overnight. The reaction was quenched with aq HCl (5%) and the aq layer was extracted twice with Et_2O. The combined organic layers were washed with aq sodium thiosulfate solution (10%), sat. aq $NaHCO_3$, dried and concentrated under reduced pressure. Distillation of the residue provided **6**.

Yield: 10.44 g (57%); colourless oil; bp 82–87 °C /32 mm Hg (lit.[7] 95 °C /13 mm Hg).

(b) Jones reagent was added dropwise to a stirred solution of the methoxy alcohol **9** (5.09 g, 39 mmol) in acetone (30 mL) until the orange colour just persisted. The acetone was removed under reduced pressure, the residue treated with H_2O (75 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were washed with H_2O (100 mL), dried, the solvent was removed and the residue distilled.

Yield: 3.46 g (69%); colourless oil; bp 82–86 °C /30 mm Hg.

IR (film): 1724, 1116 cm^{-1}.

^1H NMR: δ = 0.91 (t, 3 H, *J* = 7.3 Hz, Me), 1.25–1.7 (m, 4 H, CH_2), 2.43 (t, 2 H, *J* = 7.4 Hz, CH_2), 3.42 (s, 3 H, OMe), 4.03 (s, 2 H, OCH_2).

MS: *m/z* (%) = 129 (50) [M – H], 97 (10), 85 (50), 81 (50), 69 (100).

Reaction of Methoxyacetic Acid with Butyllithium

BuLi 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 anhyd THF (50 mL) at 0 °C under a nitrogen atmosphere. The resulting mixture was stirred under nitrogen at r.t. overnight, then added slowly, via a cannula, to rapidly stirred aq HCl (5%, 50 mL). The aq layer was extracted with Et_2O (2 × 50 mL) and the combined organic layers were dried and concentrated under reduced pressure. Removal of the solvent and distillation of the residue gave a product whose spectral data indicated that it was a mixture of **6** and **7**.

Yield: 0.54 g; yellow oil.

IR (film): 3436, 1734, 1458, 1198, 1126 cm^{-1}.

^1H NMR: δ = 0.7–1.7 (br), 2.4 (m), 3.35 (s), 3.8 (s), 4.0 (s).

1-Bromo-2-hexanol (8)

A solution of 1-hexene (6.73 g, 80 mmol) and H_2O (2.9 mL, 161 mmol) in DMSO (100 mL) was cooled to 10 °C. With stirring, NBS (29.0 g, 163 mmol) was added in one portion. The mixture was stirred at r.t. for 1 h, poured into dilute aq $NaHCO_3$ (200 mL) and extracted with Et_2O (2 × 50 mL). The combined organic extracts were washed with H_2O (3 × 50 mL), dried and the solvent was removed.

Yield: 13.92 g (96%); pale yellow oil.[8]

IR (film): 3000–3500, 1040 cm^{-1}.

^1H NMR: δ = 0.92 (t, 3 H, *J* = 6.8 Hz, Me), 1.3–1.6 (m, 6 H, CH_2), 2.34 [br s (exchanges with D_2O), 1 H, OH], 3.39 (dd, 1 H, *J* = 7.0, 10.4 Hz, 1 H of CH_2Br), 3.55 (dd, 1 H, *J* = 3.2, 10.4 Hz, 1 H of CH_2Br), 3.79 (m, 1 H, C*H*OH).

MS: *m/z* (%) = 179/181 (1) [M], 163/165 (50), 123/125 (30), 87 (100).

1-Methoxy-2-hexanol (9)

Sodium (0.84 g, 36 mmol) was added portionwise to a solution of the bromohydrin **8** (3.29 g, 18 mmol) in anhyd MeOH (20 mL) and the resulting mixture refluxed under an atmosphere of nitrogen for 3 h. The reaction mixture was cooled, H_2O (20 mL) added, and the resulting solution extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried and the solvent was removed.

Yield: 2.00 g (84%); pale yellow oil.[9]

IR (film): 3000–3500, 1060 cm^{-1}.

^1H NMR: δ = 0.91 (t, 3 H, *J* = 7.3 Hz, Me), 1.3–1.5 (m, 6 H, CH_2), 2.66 [br s (exchanges with D_2O), 1 H, OH], 3.24 (dd, 1 H, *J* = 8.0, 9.6 Hz, 1 H of OCH_2), 3.39 (s, 3 H, OMe), 3.41, (dd, 1 H, *J* = 8.0, 9.6 Hz, 1 H of OCH_2), 3.78 (m, 1 H, C*H*OH).

MS: *m/z* (%) = 131 (2) [M – H], 115 (20), 87 (50), 69 (100).

3-Methoxymethyl-1-trimethylsilylhept-1-yn-3-ol (11)

BuLi (2.5 M in hexanes; 8.5 mL, 21 mmol) was added dropwise to a stirred solution of trimethylsilylacetylene (2.26 g, 23 mmol) in anhyd THF (40 mL) at –70 °C. The resulting solution was stirred at this temperature for 10 min, followed by the slow addition of ketone **6** (2.50 g, 19 mmol) in anhyd THF (10 mL) at –70 °C. The mixture was stirred at –70 °C for 30 min and then quenched at this temperature with sat. aq NH_4Cl (40 mL). The organic phase was separated and combined with ethereal extracts of the aq phase. The combined organic extracts were dried and the solvent was removed.

Yield: 2.16 g (50%); colourless liquid; bp 52–54 °C /0.03 mm Hg.

IR (film): 3200–3600, 2140, 1250 cm^{-1}.

^1H NMR: δ = 0.17 (s, 9 H, $SiMe_3$), 0.92 (t, 3 H, *J* = 7.3 Hz, Me), 1.3–1.7 (m, 6 H, CH_2), 2.80 [br s (exchanges with D_2O), 1 H, OH], 3.38 (d, 1 H, *J* = 9.3 Hz, 1 H of OCH_2), 3.46 (s, 3 H, OMe), 3.48 (d, 1 H, *J* = 9.3 Hz, 1 H of OCH_2).

MS: *m/z* (%) = 228, (1) [M], 212 (30), 211 (100), 184 (40), 183 (100).

HRMS: *m/z* calcd for $C_{12}H_{24}0Si$ [M – O]: 212.1596; found: 212.1604.

3-Methoxymethylhept-1-yn-3-ol (10)

(a) TBAF in THF (1 M; 2 mL, 2 mmol) was added dropwise to a stirred solution of the alkynol **11** (0.20 g, 0.88 mmol) in THF (2 mL) at r.t. under an atmosphere of nitrogen and the mixture was stirred for 30 min. The solvent was removed under reduced pressure and the residue was extracted with Et_2O (20 mL). The extracts were washed with H_2O (6 mL), aq HCl (10%; 6 mL), H_2O (6 mL), dried, and evaporated to give a colourless oil which was chromatographed [EtOAc (18%) in hexane] to give **10**.

Yield: 74 mg (54%); colourless oil; bp 105 °C /25 mm Hg.

IR (film): 3444, 3304, 2120, 1112 cm^{-1}.

^1H NMR: δ = 0.7–1.6 (br, 9 H, Bu), 2.2 (s, 1 H, alkyne H), 2.5 (br, 1 H, OH), 3.3 (s, 2 H, CH_2O), 3.4 (s, 3 H, OMe).

MS: *m/z* (%) = 111 (30) [M – CH_2OMe], 26 (100).

Anal. Calcd for $C_9H_{16}O$: C, 69.2; H, 10.3. Found: C, 68.6; H, 9.9.

(b) The ketone **6** (17.00 g, 0.13 mol) in anhyd THF (25 mL) was added slowly to an ice-cooled, stirred solution of ethynylmagnesium chloride[10] (150 mL) under an atmosphere of nitrogen and the

resulting mixture was allowed to warm to r.t. and then stirred for 20 h. The reaction was quenched with sat. aq NH_4Cl and the aq layer was extracted twice with Et_2O. The combined organic layers were dried and evaporated to give an oil which was chromatographed [Et_2O (35%) in hexane] to give **10**.

Yield: 15.90 g (78%).

3-Chloro-3-methoxymethyl-1-trimethylsilyl-1-hexyne (12)
The alkynol **11** (4.35 g, 19 mmol) was added to a stirred mixture of cuprous chloride (0.79 g, 7.9 mmol), calcium chloride (1.06 g, 9.5 mmol) and copper bronze powder (0.60 g) in aq HCl (concd; 50 mL) and the resulting mixture stirred at r.t. for 96 h. The mixture was extracted with CH_2Cl_2 (3 × 40 mL); the combined organic extracts were washed with aq HCl (concd; 2 × 40 mL) and H_2O (3 × 30 mL), dried and the solvent was removed. The residue was purified by flash chromatography (light petroleum–EtOAc, 95:5) to afford **12**.

Yield: 3.44 g (73%); colourless oil.

^{1}H NMR: δ = 0.18 (s, 9 H, $SiMe_3$), 0.94 (t, 3 H, *J* = 7.3 Hz, Me), 1.3–1.4 (m, 2 H, CH_2), 1.5–1.6 (m, 2 H, CH_2), 1.9–2.0 (m, 2 H, CH_2), 3.49 (s, 3 H, OMe), 3.64 (s, 2 H, OCH_2).

MS *m*/*z* (%) = 247/249 (15) [M + H], 231/233 (15), 211 (100), 180 (80).

HRMS: *m*/*z* calcd for $C_{12}H_{23}ClOSi$: 246.1207; found: 246.1194.

3-Butyl-1-trimethylsilylhept-1-yn-3-ol
BuLi (2.5 M in hexanes; 3.10 mL, 7.7 mmol) was added dropwise to a stirred solution of trimethylsilylacetylene (0.83 g, 8.5 mmol) in anhyd THF (15 mL) at –70 °C. The resulting mixture was stirred at this temperature for 10 min, followed by the slow addition of a solution of 5-nonanone (1.00 g, 7 mmol) in anhyd THF (5 mL) at –70 °C. The mixture was stirred at this temperature for 20 min and quenched by the addition of sat. aq NH_4Cl (15 mL). The organic phase was separated and combined with ethereal extracts of the aq phase. The combined organic extracts were dried and the solvent was removed. The residue was purified by flash chromatography (light petroleum–EtOAc, 85:15) to provide the alkynol.

Yield: 1.42 g (85%); colourless oil.

IR (film): 3250–3600, 2135, 1255 cm^{-1}.

^{1}H NMR: δ = 0.16 (s, 9 H, $SiMe_3$), 0.93 (t, 6 H, *J* = 6.8 Hz, Me), 1.25–1.75, (m, 8 H, CH_2), 2.10 [br s (exchanges with D_2O), 1 H, OH], 2.40 (t, 4 H, *J* = 7.3 Hz, CH_2).

MS: *m*/*z* (%) = 223 (80) [M – OH], 183 (100), 150 (15).

3-Butyl-3-chloro-1-trimethylsilyl-1-heptyne (14)
The above dibutylcarbinol (1.19 g, 5 mmol) was added to a stirred mixture of cuprous chloride (0.21 g, 2.1 mmol), calcium chloride (0.28 g, 2.5 mmol) and copper bronze powder (0.20 g) in aq HCl (concd; 30 mL) and the resulting mixture stirred at r.t. for 48 h. The mixture was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts were washed with aq HCl (concd; 2 × 15 mL) and H_2O (3 × 10 mL), dried and the solvent was removed. The residue was purified by flash chromatography (light petroleum–EtOAc, 95:5) to give **14**.

Yield: 1.17 g (91%); colourless oil.

IR (film): 2140, 1250 cm^{-1}.

^{1}H NMR: δ = 0.18, (s, 9 H, $SiMe_3$), 0.94 (t, 6 H, *J* = 7.3 Hz, Me), 1.25–1.7 (m, 8 H, CH_2), 1.89 (m, 4 H, CH_2).

MS: *m*/*z* (%) = 258/260 (10) [M], 243/245 (15), 225 (45), 224 (100), 223 (100).

HRMS: *m*/*z* calcd for $C_{14}H_{17}ClSi$: 258.1570; found: 258.1571.

4-Substituted *N*-[3-(Methoxymethyl)hept-1-yn-3-yl]anilines 13 a–e
A literature procedure[1f] was used to prepare the following compounds.

***N*-[3-(Methoxymethyl)hept-1-yn-3-yl]-4-methylaniline (13a)**
Yield: 1.20 g (61%); yellow oil.

^{1}H NMR: δ = 0.92 (t, 3 H, *J* = 7.2 Hz, Me), 1.2–1.9 (m, 6 H, CH_2), 2.25 (s, 3 H, ArMe), 2.42 (s, 1 H, C≡CH), 3.37 (s, 3 H, OMe), 3.48 (d, 1 H, *J* = 9.2 Hz, 1 H of OCH_2), 3.55 (d, 1 H, *J* = 9.2 Hz, 1 H of OCH_2), 3.85 [br s (exchanges with D_2O), 1 H, NH], 6.92 (d, 2 H, *J* = 8.4 Hz, ArH), 6.98 (d, 2 H, *J* = 8.4 Hz, ArH).

MS: *m*/*z* (%) = 245 (5) [M], 200 (100), 158 (10), 156 (10).

HRMS: *m*/*z* calcd for $C_{16}H_{23}NO$: 245.1780; found: 245.1787.

***N*-[3-(Methoxymethyl)hept-1-yn-3-yl]-4-methoxyaniline (13b)**
Yield: 20 mg (38%); orange oil.

IR ($CDCl_3$): 3300, 3125, 1600, 1505, 1105 cm^{-1}.

^{1}H NMR: δ = 0.92 (t, 3 H, *J* = 7.1 Hz, Me), 1.25–1.55 (m, 4 H, CH_2), 1.65–1.85 (m, 2 H, CH_2), 2.41 (s, 1 H, C≡CH), 3.39 (s, 3 H, OMe), 3.43 (d, 1 H, *J* = 9.2 Hz, 1 H of OCH_2), 3.51 (d, 1 H, *J* = 9.2 Hz, 1 H of OCH_2), 3.65 [br s (exchanges with D_2O), 1 H, NH], 3.76 (s, 3 H, OMe), 6.78 (d, 2 H, *J* = 8.8 Hz, ArH), 7.00 (d, 2 H, *J* = 8.8 Hz, ArH).

MS: *m*/*z* (%) = 261 (10) [M], 216 (100), 172 (10), 158 (10), 122 (15).

HRMS: *m*/*z* calcd for $C_{16}H_{23}NO_2$: 261.1729; found: 261.1731.

Ethyl *N*-[3-(Methoxymethyl)hept-1-yn-3-yl]-4-aminobenzoate (13c)
Yield: 50 mg (41%); orange oil.

^{1}H NMR: δ = 0.91 (t, 3 H, *J* = 7.1 Hz, Me), 1.3–2.1 (m, 6 H, CH_2), 1.35 (t, 3 H, *J* = 7.1 Hz, OCH_2*Me*), 2.51 (s, 1 H, C≡CH), 3.38 (s, 3 H, OMe), 3.53 (d, 1 H, *J* = 9.2 Hz, 1 H of OCH_2), 3.62 (d, 1 H, *J* = 9.2 Hz, 1 H of OCH_2), 4.31 (q, 2 H, *J* = 7.1 Hz, O*C*H_2Me), 4.54 [br s (exchanges with D_2O), 1 H, NH], 6.92 (d, 2 H, *J* = 8.8 Hz, ArH), 7.84 (d, 2 H, *J* = 8.8 Hz, ArH).

MS: *m*/*z* (%) = 303 (1) [M], 259 (20), 258 (100), 230 (5), 185 (3).

HRMS: *m*/*z* calcd for $C_{18}H_{25}NO_3$: 303.1834; found: 303.1818.

***N*-[3-(Methoxymethyl)hept-1-yn-3-yl]-4-bromoaniline (13d)**
Yield: 0.30 g (48%); orange oil.

^{1}H NMR: δ = 0.92 (t, 3 H, *J* = 7.3 Hz, Me), 1.3–1.9 (m, 6 H, CH_2), 2.46 (s, 1 H, C≡CH), 2.70 [br s (exchanges with D_2O), 1 H, NH], 3.39 (s, 3 H, OMe), 3.49 (d, 1 H, *J* = 9.3 Hz, 1 H of OCH_2), 3.57 (d, 1 H, *J* = 9.3 Hz, 1 H of OCH_2), 6.87 (d, 2 H, *J* = 8.8 Hz, ArH), 7.26 (d, 2 H, *J* = 8.8 Hz, ArH).

MS: *m*/*z* (%) = 309/311 (10) [M], 265/267 (20), 264/266 (100), 251 (15).

HRMS: *m*/*z* calcd for $C_{15}H_{20}BrNO$: 309.0728; found: 309.0741.

***N*-[3-(Methoxymethyl)hept-1-yn-3-yl]-4-acetamidoaniline (13e)**
Yield: 0.079 g (69%); pale yellow needles; mp 106–108 °C.

IR ($CDCl_3$): 3440, 3370, 3300, 1675, 1600, 1505 cm^{-1}.

^{1}H NMR: δ = 0.92 (t, 3 H, *J* = 7.0 Hz, Me), 1.2–1.9 (m, 6 H, CH_2), 2.11 (s, 3 H, COMe), 2.45 (s, 1 H, C≡CH), 3.38 (s, 3 H, OMe), 3.47 (d, 1 H, *J* = 9.2 Hz, 1 H of OCH_2), 3.55 (d, 1 H, *J* = 9.2 Hz, 1 H of OCH_2), 3.9 [br s (exchanges with D_2O), NH amine), 6.95 (d, 2 H, *J* = 8.7 Hz, ArH), 7.30, (d, 2 H, *J* = 8.7 Hz, ArH), 7.67 [br s (exchanges with D_2O), 1 H, NH].

MS: *m/z* (%) = 288 (25) [M], 244 (20), 243 (100), 231 (5), 201 (7), 149 (15).

HRMS: *m/z* calcd for $C_{17}H_{24}N_2O_2$: 288.1838; found: 288.1846.

2-Butyl-2-methoxymethyl-6-methyl-1,2-dihydroquinoline (15) and 2-Butyl-6-methylquinoline (16)

The *N*-substituted aniline **13a** was cyclised using a literature procedure.[1f] The residue was purified by flash chromatography (light petroleum–EtOAc, 90:10) to give **15**.

Yield: 0.14 g (21%); unstable orange oil.

^{1}H NMR: δ = 0.95 (t, 3 H, *J* = 7.3 Hz, Me), 1.2–1.6 (m, 6 H, CH_2), 2.24 (s, 3 H, ArMe), 3.15 (d, 1 H, *J* = 8.7 Hz, 1 H of OCH_2), 3.31 (s, 3 H, OMe), 3.40 (d, 1 H, *J* = 8.7 Hz, 1 H of OCH_2), 5.28 (d, 1 H, *J* = 8.9 Hz, C=CH), 6.32 (d, 1 H, *J* = 8.9 Hz, C=CH), 6.65 (d, 1 H, *J* = 1.8 Hz, ArH), 6.74 (dd, 1 H, *J* = 1.8, 9.6 Hz, ArH), 6.90 (d, 1 H, *J* = 9.6 Hz, ArH).

MS: *m/z* (%) = 246 (15) [M + H], 245 (10) [M], 244 (10) [M – H].

On standing, **15** converted to **16**, which was also isolated from the above reaction.

Yield: 0.16 g (24%); orange oil.

IR (film): 1695, 1605, 1555, 1500 cm^{-1}.

^{1}H NMR: δ = 0.95 (t, 3 H, *J* = 7.3 Hz, Me), 1.35–1.50 (m, 2 H, CH_2), 1.65–1.85 (m, 4 H, CH_2), 2.50 (s, 3 H, ArMe), 2.90–3.00 (m, 2 H, CH_2), 7.24 (d, 1 H, *J* = 8.4 Hz, ArH), 7.49 (m, 2 H, ArH), 7.94 (m, 2 H, ArH).

MS: *m/z* (%) = 200 (5) [M + H], 199 (5) [M], 198 (5) [M – H], 184 (10), 170 (25), 157 (100).

HRMS: *m/z* calcd for $C_{14}H_{17}N$: 199.1361; found: 199.1355.

6-Substituted 2-Butyl-2-methoxymethyl-1-trifluoroacetyl-1,2-dihydroquinolines 17a,b

A stirred mixture of the *N*-substituted aniline **13a** or **13b** (2.3 mmol) and cuprous chloride (200 mg) in toluene (10 mL) was refluxed under an atmosphere of nitrogen for 30 min. The reaction mixture was cooled and trifluoroacetic anhydride (0.5 mL, 3.5 mmol) was added under an atmosphere of nitrogen. The resulting mixture was stirred under an atmosphere of nitrogen at r.t. for 1.5 h. H_2O (15 mL) was added and the organic phase separated and combined with the CH_2Cl_2 extracts of the aq phase. The combined organic extracts were dried and the solvent was removed. The residue was purified by flash chromatography.

2-Butyl-2-methoxymethyl-6-methyl-1-trifluoroacetyl-1,2-dihydroquinoline (17a)

Yield: 0.49 g (63%); orange oil, after elution with light petroleum–EtOAc (85:15).

IR (film): 1690, 1600, 1570, 1500 cm^{-1}.

^{1}H NMR: δ = 0.81 (t, 3 H, *J* = 6.9 Hz, Me), 1.2–1.6 (m, 6 H, CH_2), 2.31 (s, 3 H, ArMe), 3.31 (s, 3 H, OMe), 3.70 (d, 1 H, *J* = 9.4 Hz, 1 H of OCH_2), 4.23 (d, 1 H, *J* = 9.4 Hz, 1 H of OCH_2), 5.81 (d, 1 H, *J* = 9.8 Hz, C=CH), 6.49 (d, 1 H, *J* = 9.8 Hz, C=CH), 6.75 (d, 1 H, *J* = 8.0 Hz, ArH), 7.14 (br s, 1 H, ArH), 7.30 (m, 1 H, ArH).

MS: *m/z* (%) = 342 (40) [M + H], 310 (40), 297 (75), 296 (100), 283 (15).

HRMS: *m/z* calcd for $C_{18}H_{22}F_3NO_2$: 341.1603; found: 341.1588.

2-Butyl-2-methoxymethyl-6-methoxy-1-trifluoroacetyl-1,2-dihydroquinoline (17b)

Yield: 60%; orange oil, after elution with light petroleum–EtOAc (80:20).

IR (CH_2Cl_2): 1690, 1605, 1550, 1510 cm^{-1}.

^{1}H NMR: δ = 0.93 (t, 3 H, *J* = 6.9 Hz, Me), 1.20–1.55 (m, 4 H, CH_2), 1.70–1.80 (m, 2 H, CH_2), 3.42 (s, 3 H, OMe), 3.68 (d, 1 H, *J* = 9.6 Hz, 1 H of OCH_2), 3.80 (s, 3 H, OMe), 4.23 (d, 1 H, *J* = 9.6 Hz, 1 H of OCH_2), 5.88 (d, 1 H, *J* = 9.4 Hz, C=CH), 6.50 (d, 1 H, *J* = 9.4 Hz, C=CH), 6.83 (d, 1 H, *J* = 8.9 Hz, ArH), 7.30–7.55 (m, 2 H, ArH).

MS: *m/z* (%) = 358 (5) [M + H], 326 (15), 312 (55), 219 (45), 173 (100), 158 (40).

2-Butyl-3,4-dichloro-2-methoxymethyl-6-methyl-1-trifluoroacetyl-1,2,3,4-tetrahydroquinoline (18)

This compound was obtained by a literature chlorination procedure on **17a**.[1f]

Yield: 57%; unstable, viscous, yellow oil.

^{1}H NMR: δ = 0.79 (t, 3 H, *J* = 7.1 Hz, Me); 1.1–1.7 (m, 6 H, CH_2), 2.40 (s, 3 H, ArMe), 3.36 (s, 3 H, OMe), 3.92 (d, 1 H, *J* = 10.3 Hz, 1 H of OCH_2), 4.26 (d, 1 H, *J* = 10.3 Hz, 1 H of OCH_2), 4.39 (d, 1 H, *J* = 6.2 Hz, CHCl), 5.60 (d, 1 H, *J* = 6.2 Hz, CHCl), 6.87 (d, 1 H, *J* = 7.8 Hz, ArH), 7.13 (dd, 1 H, *J* = 1.4, 7.8 Hz, ArH), 7.48 (d, 1 H, *J* = 1.4 Hz, ArH).

MS: *m/z* (%) = 411/413/415 (5) [M], 366/368/370 (100), 330/332 (10), 296 (50), 294 (20).

HRMS: *m/z* calcd for $C_{18}H_{22}Cl_2F_3NO_2$: 411.0980; found: 411.1040.

2-Butyl-3-chloro-2-methoxymethyl-6-methyl-1-trifluoroacetyl-1,2,3,4-tetrahydroquinoline (19)

This compound was prepared by a literature selective dechlorination procedure on **18**.[1f]

Yield: 91%; a viscous, pale yellow oil.

^{1}H NMR: δ = 0.80 (t, 3 H, *J* = 7.2 Hz, Me), 1.0–1.6 (m, 6 H, CH_2), 2.24 (s, 3 H, ArMe), 3.06 (dd, 1 H, *J* = 4.3, 16.0 Hz, 1 H of CH_2), 3.35 (s, 3 H, OMe), 3.53 (dd, 1 H, *J* = 7.2, 16.0 Hz, 1 H of CH_2), 3.93 (d, 1 H, *J* = 10.2 Hz, 1 H of OCH_2), 4.22 (d, 1 H, *J* = 10.2 Hz, 1 H of OCH_2), 4.28 (dd, 1 H, *J* = 4.3, 7.2 Hz, CHCl), 6.8–7.0 (m, 3 H, ArH).

MS: *m/z* (%) = 377/379 (25) [M], 332/334 (100), 296 (30).

HRMS: *m/z* calcd for $C_{18}H_{25}ClF_3NO_2$: 377.1369; found: 377.1376.

2-Butyl-3-chloro-2-methoxymethyl-6-methyl-1,2,3,4-tetrahydroquinoline (20)

A solution of the trifluoroacetamide **19** (50 mg, 0.13 mmol) in KOH in MeOH (10%; 2 mL) was stirred at r.t. for 2.5 h. H_2O (5 mL) was added and the mixture extracted with CH_2Cl_2 (4 × 10 mL). The combined organic extracts were dried and the solvent was removed. The residue was purified by flash chromatography (light petroleum–EtOAc, 90:10) to provide **20**.

Yield: 28 mg (75%); colourless prisms; mp 65–67 °C.

IR ($CDCl_3$): 3400, 1605, 1500 cm^{-1}.

^{1}H NMR: δ = 0.89 (t, 3 H, *J* = 9.1 Hz, Me), 1.25–1.36 (m, 4 H, CH_2), 1.54–1.73 (m, 2 H, CH_2), 2.21 (s, 3 H, ArMe), 3.00 (dd, 1 H, *J* = 6.6, 17.1 Hz, 1 H of CH_2), 3.27 (dd, 1 H, *J* = 5.2, 17.1 Hz, 1 H of CH_2), 3.35 (s, 3 H, OMe), 3.47 (d, 1 H, *J* = 8.9 Hz, 1 H of OCH_2), 3.52 (d, 1 H, *J* = 8.9 Hz, 1 H of OCH_2), 3.90 [br s (exchanges with D_2O), 1 H, NH], 4.32 (dd, 1 H, *J* = 5.2, 6.6 Hz, CHCl), 6.47 (d, 1 H, *J* = 8.0 Hz, ArH), 6.79 (s, 1 H, ArH), 6.83 (d, 1 H, *J* = 8.0 Hz, ArH).

MS *m/z* (%) = 281/283 (11) [M], 236/238 (84), 200 (41), 170 (19), 157 (100).

HRMS: *m/z* calcd for $C_{16}H_{24}ClNO$: 281.1546; found: 281.1559.

Acknowledgment

NMW gratefully acknowledges the award of an Australian Postgraduate Research Award (Priority).

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