Aust. J. Chem., 1994, **47**, 2109–2117

Attempted Heterocyclic Syntheses Through Electrophilic Ring Closure Reactions of 2-Allylaniline Systems Containing Larger Side Chains

Craig L. Francis and A. David Ward

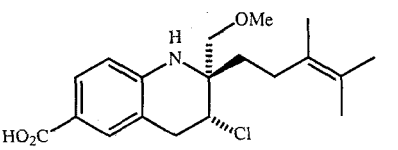
Department of Chemistry, The University of Adelaide, Adelaide, S.A. 5005.

Abstract

The electrophile-initiated cyclization of some 2-allylanilines and their amide derivatives has been further investigated. Although 2-allylanilines with small, allylic substituents such as methyl reacted with iodine to yield 3-iodo-1,2,3,4-tetrahydroquinolines the 2-allylanilines with larger substituents related to those of virantmycin provided low yields of the tetrahydroquinoline as part of a complex product mixture.

Introduction

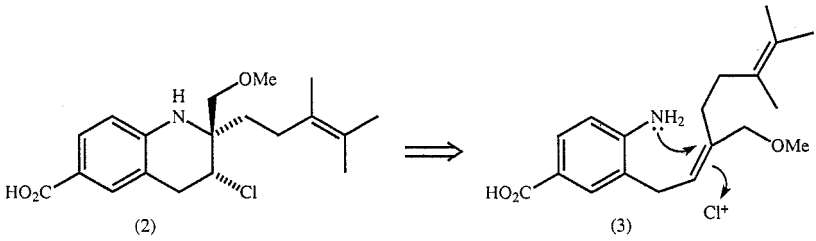
We have been investigating synthetic approaches to the novel antibiotic virantmycin (1)[1–9] for some time with our aim being to develop general routes in order to prepare a variety of structural analogues for use in structure–activity relationships. Part of our methodology[10–12] involves the electrophile-initiated cyclization of 2-(3,3-disubstituted allyl)aniline systems (Scheme 1).



(1)

[1] Omura, S., Nakagawa, A., Hashimoto, H., Oiwa, R., Iwai, Y., Hirano, A., Shibukawa, N., and Kojima, Y., *J. Antibiot.*, 1980, **33**, 1395.
[2] Nakagawa, A., and Omura, S., *Tetrahedron Lett.*, 1981, **22**, 2199.
[3] Hirano, A., Hashimoto, H., Iwai, Y., Kojima, Y., Miyazaki, N., Nakagawa, A., Oiwa, R., Omura, S., Takahashi, Y., and Shibukawa, N., *J. Antibiot.*, 1981, **34**, 1408.
[4] Hill, M. L., and Raphael, R. A., *Tetrahedron Lett.*, 1986, **27**, 1293.
[5] Hill, M. L., and Raphael, R. A., *Tetrahedron*, 1990, **46**, 4587.
[6] Morimoto, Y., Oda, K., Shirahama, H., Matsumoto, T., and Omura, S., *Chem. Lett.*, 1988, 909.
[7] Morimoto, Y., Matsuda, F., and Shirahama, H., *Tetrahedron Lett.*, 1990, **31**, 6031.
[8] Morimoto, Y., Matsuda, F., and Shirahama, H., *Synlett*, 1991, 201.
[9] Pearce, C. M., and Sanders, J. K. M., *J. Chem. Soc., Perkin Trans. 1*, 1990, 409.
[10] Raner, K. D., Skelton, B. W., Ward, A. D., and White, A. H., *Aust. J. Chem.*, 1990, **43**, 609.
[11] Raner, K. D., and Ward, A. D., *Aust. J. Chem.*, 1991, **44**, 1749.
[12] De Silva, A. N., Francis, C. L., and Ward, A. D., *Aust. J. Chem.*. 1993, **46**, 1657.

Manuscript received 15 April 1994 0004-9425/94/112109$05.00

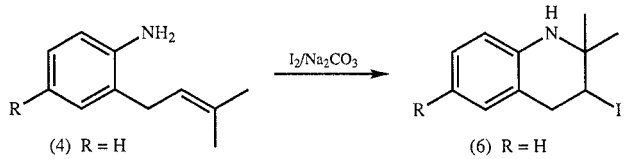


(2) (3) Scheme 1

Initially the stereochemistry suggested for virantmycin was that shown in (2) and this was assumed in designing the methodology for the cyclization of suitable allylanilines (3). Our early results on model compounds in this area of electrophile-initiated cyclization have been reported.[11,12] This paper describes our results from further, related studies which use the larger and oxygen-containing substituents that are more closely related to those in virantmycin.

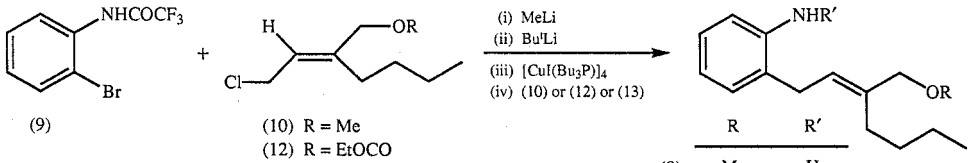
Results and Discussion

The iodine-initiated electrophilic ring closure of allylanilines (4) and (5), which contain the relatively small methyl substituents, produces the 3-iodotetrahydroquinolines (6) and (7) respectively (Scheme 2).[11]



(4) R = H
(5) R = CHO
(6) R = H
(7) R = CHO
Scheme 2

We wished to extend the scope of this reaction to include compounds with larger allylic substituents as these would be required for synthesis of virantmycin and close structural analogues. The iodine-initiated cyclization method was applied to allylaniline (8), prepared as shown in Scheme 3.



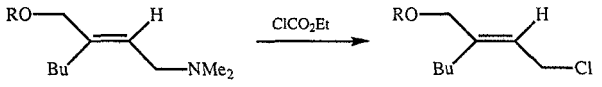
(9)
(10) R = Me
(12) R = EtOCO
(13) R = BuᵗMe2Si

	R	R′
(8)	Me	H
(11)	Me	$COCF_3$
(14)	EtOCO	$COCF_3$
(15)	BuᵗMe2Si	$COCF_3$

Scheme 3

The aryl cuprate species of (9), prepared by the reported procedure,[11] underwent reaction with chloride (10) in tetrahydrofuran at −50° to give allylbenzene (11). Analogous reactions with allylic chlorides (12) and (13) afforded the allylbenzenes (14) and (15), respectively. These results showed that an aryl cuprate species can be efficiently coupled with allylic chlorides to produce allylbenzenes and that the reaction is tolerant of a variety of functional groups.

The chlorides (10), (12) and (13) were prepared from the reported[12] compounds (16) and (17). Reaction of (16) with excess ethyl chloroformate in benzene[13] afforded chloride (10). Treatment of the amino alcohol (17) with ethyl chloroformate gave the chloro carbonate (12) and conversion of (17) into its t-butyldimethylsilyl ether (18) followed by treatment with ethyl chloroformate provided the silylated allylic chloride (13) (Scheme 4).

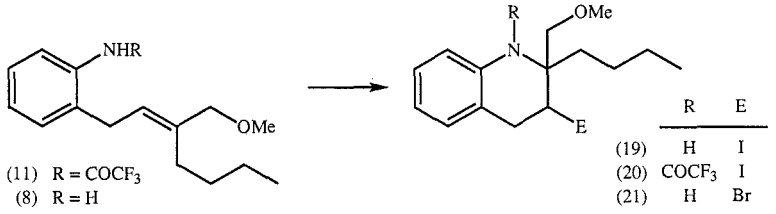


(16) R = Me
(17) R = H
(18) R = Bu^{t}Me$_2$Si

(10) R = Me
(12) R = EtOCO
(13) R = Bu^{t}Me$_2$Si

Scheme 4

The trifluoroacetamide (11) was hydrolysed to the free amine (8) by methanolic potassium hydroxide. Treatment of (8) with 1 equiv. of iodine and sodium carbonate in dichloromethane for 4 h according to the reported[11] procedure (Scheme 5) resulted in an intractable product mixture. The ^{1}H n.m.r. spectrum of this product lacked a signal near δ 4·4 expected[11] for the desired product. The reaction was repeated in darkness and with 2 equiv. of iodine but returned the same outcome. Treatment of the allylaniline (8) with 2 equiv. of iodine and sodium carbonate in dichloromethane at 0° for 30 min returned starting material and at room temperature for 1 h gave an intractable product.



(11) R = COCF$_3$
(8) R = H

	R	E
(19)	H	I
(20)	COCF$_3$	I
(21)	H	Br

Scheme 5

The iodotetrahydroquinoline (6) was unstable to distillation,[11] so it was possible that the desired product (19) in the above reactions either was thermally unstable or decomposed during attempts to isolate it. It was thought that the conversion of the iodotetrahydroquinoline into the corresponding trifluoroacetamide (20) *in situ* may confer extra stability to the molecule, thus enabling its isolation, assuming of course that cyclization does occur. A reaction on (8) by using the initial procedure, but quenching the product with an excess of trifluoroacetic anhydride gave material that yielded four fractions after flash chromatography. The component of highest R_F was impure and in low yield but showed ^{1}H n.m.r. spectral characteristics expected of the desired product (20). These included a doublet of doublets at δ 4·6 attributable[11] to the proton geminal to the iodine atom and coupled with the benzylic methylene protons, a strong methoxy singlet resonance at 3·35, a doublet at 3·5 attributable to the benzylic methylene protons, a set of aromatic signals very similar in appearance to those of compound (6) and the absence of allylic methylene and vinylic proton resonances. The mass spectrum showed a

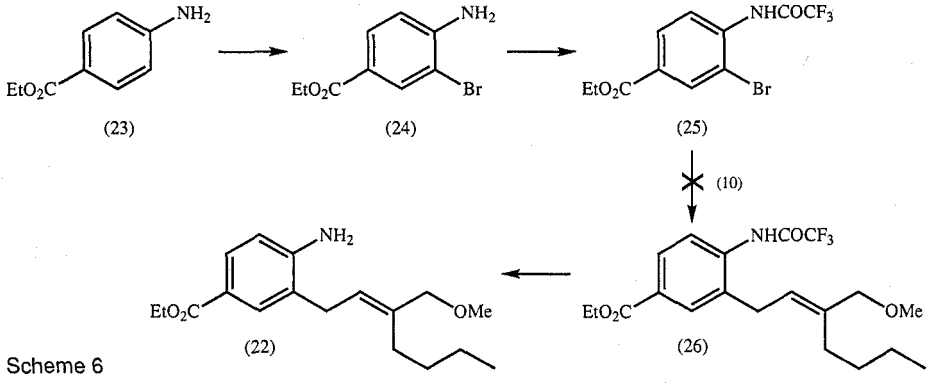
[13] Mornet, R., and Gouin, L., *Synthesis*, 1977, 786.

strong molecular ion at m/z 455, the value expected for (20). Another fraction of lower R_F corresponded by t.l.c. and ^{1}H n.m.r. spectroscopy to (11), resulting from trifluoroacetylation of the starting material. The other two fractions showed poorly resolved infrared and ^{1}H n.m.r. spectra, indicating complex mixtures of products. Changes in the aromatic region of the ^{1}H n.m.r. spectra suggested that these fractions may contain material that resulted from ring substitution. A considerable amount of much more polar material remained on the column, suggesting that a significant amount of decomposition had occurred.

Treatment of the allylaniline (8) with 1 equiv. of bromine and sodium carbonate in dichloromethane in darkness at 0° for 30 min resulted in the formation of a complex mixture of products, as evidenced by t.l.c. data and a ^{1}H n.m.r. spectrum with few clearly resolved signals. The ^{1}H n.m.r. spectrum did show resonances due to the starting allylaniline (8) and a weak multiplet at δ 4·6. This resonance could be attributed to the hydrogen attached to the carbon bearing the bromine in (21), indicating a low yield of cyclized product. However, increased complexity in the region δ 6·35–7·4 indicated the possibility of bromination of the aromatic ring. The mass spectrum showed a peak at m/z 233 corresponding to the molecular ion for (8) and others at m/z 311 and 313 which could correspond to (21) or a product resulting from monobromination of the aromatic ring.

Treatment of the less nucleophilic trifluoroacetamide (11) with 2 equiv. of iodine and sodium carbonate in dichloromethane or in a two-phase system resulted in isolation of starting material only.

Since the iodine treatment resulted in a complex mixture of products from the amine (8) and failed to cause a reaction with trifluoroacetamide (11), a compound of intermediate reactivity was considered as substrate for this reaction. The ester (22), which has the nitrogen lone pair delocalized throughout the aromatic ring and ester function was considered to be appropriate although it was recognized that the presence of the ester group may complicate the cuprate coupling reaction. The fact that the carbonate group of the allylic chloride (12) was found to be compatible with the coupling conditions was encouraging. The sequence of reactions chosen to prepare (22) was that shown in Scheme 6.



Scheme 6

Attempted preparation of (26) via formation of the aryl cuprate species of (25) and subsequent reaction with (10) by the usual procedure[11] resulted in the formation of an intractable mixture. The ^{1}H n.m.r. spectrum of the product

showed no significant ethyl ester resonances; this indicated that the ester group had not survived the reaction.

In summary, whilst the simple model compounds, dimethylallylanilines (4) and (5), underwent iodine-initiated cyclization to produce iodotetrahydroquinolines (6) and (7), respectively,[11] compounds (11) and (8) which have larger allylic substituents, either failed to produce any cyclized product or only provided a very low yield of the desired iodotetrahydroquinoline. The larger groups around the allylic carbon appear to hinder the cyclization sufficiently that other processes become competitive. It is also possible that the oxygen atom of the methoxymethyl side chain is affecting the course of these reactions by coordinating to the reagents. Our attention has now turned to other, and successful, means[14] of forming the desired 3-substituted tetrahydroquinoline systems.

Experimental

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Microanalyses were performed by the Canadian Microanalytical Service, Vancouver. Flash chromatography[15] refers to nitrogen-pressure-driven rapid chromatography with Amicon Matrex Silica, pore diameter 60 Å. Squat column chromatography refers to 'dry column' flash chromatography[16] with Merck Kieselgel HF_{254} silica. Drying and other purification of organic solvents was accomplished by standard laboratory procedures.[17,18] All organic extracts were dried over anhydrous magnesium sulfate unless otherwise stated. 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 on a Bruker WP80DS spectrometer operating at 20·1 or 80 MHz, respectively, or a Bruker CXP300 or Bruker ACP300 spectrometer operating at 75·47 or 300 MHz. Mass spectra were recorded on an AEI MS3074 spectrometer operating at 70 eV. Only the major fragments are given with their relative abundances shown in parentheses.

(E)-*1-Chloro-3-methoxymethylhept-2-ene (10)*

This was prepared by adapting the method of Mornet and Gouin.[13] Thus, the allylic amine (16)[12] (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* (10) (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}. ^{1}H n.m.r. δ ($CDCl_3$) 0·7–1·6, br, $CH_3CH_2CH_2$; 2·1, m, $C{=}CCH_2$; 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=CH. Mass spectrum *m/z* 176 (3%)/178 (M, 1), 141 (47), 121 (22), 119 (95), 114 (17), 109 (15), 85 (33), 41 (100).

(E)-N-*(3-t-Butyldimethylsilyloxymethyl-2-hepten-1-yl)*-N,N-*dimethylamine (18)*

Chlorodimethyl-t-butylsilane (4·80 g, 32·1 mmol) in anhydrous tetrahydrofuran (50 ml) was slowly added to a stirred mixture of the alcohol (17)[12] (5·00 g, 29·2 mmol), triethylamine (3·50 g,

[14] Williamson, N. M., March, D. R., and Ward, A. D., unpublished data.
[15] Still, W. C., Kahn, M., and Mitra, A., *J. Org. Chem.*, 1978, **43**, 2923.
[16] Harwood, L. M., *Aldrichimica Acta*, 1985, **18**, 25.
[17] Vogel, A. I., 'A Textbook of Practical Organic Chemistry Including Qualitative Organic Analysis' 3rd Edn (Longman: London 1977).
[18] Perrin, D. D., Armarego, W. L. F., and Perrin, D. R., 'Purification of Laboratory Chemicals' 2nd Edn (Pergamon: Oxford 1980).

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 were 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%; *m/z* 285·2497. $C_{16}H_{35}NOSi$ requires C, 67·3; H, 12·4%; *m/z* 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, $C{=}CCH_2$; 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=CH. 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)-*3-t-Butyldimethylsilyloxymethyl-1-chlorohept-2-ene (13)*

The silyloxy(amino)alkene (18) (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* (13) (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, $C{=}CCH_2$; 4·05, s, CH_2O, 4·1, d, *J* 8 Hz, CH_2Cl; 5·65, t, *J* 8 Hz, C=CH. Mass spectrum *m/z* 276/278 (M, <1%), 261 (6)/263 (2), 241 (37), 219 (100).

(E)-*2-(2-Chloroethylidene)hexyl Ethyl Carbonate (12)*

The allylic amino alcohol (17)[12] (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* (12) (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, $C{=}CCH_2$; 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=CH. Mass spectrum *m/z* 234 (0·3%)/236 (M, 0·1), 199 (40), 109 (100).

N-*[2-(3-Methoxymethylhept-2-en-1-yl)phenyl]trifluoroacetamide (11)*

This compound was prepared by adapting the procedure of Raner.[11] A solution of trifluoroacetamide (9) (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 t-butyllithium in pentane (1·3 M, 25·85 ml, 33·6 mmol). After stirring for 1 min, tetrakis[iodo(tributylphosphine)copper(I)][19] (6·00 g, 14·96 mmol copper) in anhydrous tetrahydrofuran (40 ml) was added, followed 5 min later by the allyllic chloride (10) (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 was 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* (11) (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, $C{=}CCH_2$; 3·25, s, OCH_3; 3·4, d, *J* 7 Hz, $ArCH_2C{=}C$; 3·8, s,

[19] Kauffman, G. B., and Teter, L. A., *Inorg. Synth.*, 1963, **7**, 9.

CH_2O; 5·45, t, *J* 7 Hz, C=CH; 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).

(E)-2-(2-Trifluoroacetamidophenyl)ethylidenehexyl Ethyl Carbonate (14)

A stirred solution of (9) (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 t-butyllithium in pentane (1·3 M, 2·58 ml, 3·36 mmol). After stirring for 1 min, tetrakis[iodo(tributylphosphine)copper(I)][19] (0·60 g, 1·50 mmol) in anhydrous tetrahydrofuran (4 ml) was added, followed 5 min later by the allylic chloride (12) (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* (14) (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_2CH_3; 2·15, m, $C=CCH_2$; 3·4, d, *J* 7 Hz, $ArCH_2C=C$; 4·1, q, *J* 7 Hz, OCH_2CH_3; 4·5, s, CH_2O; 5·55, t, *J* 7 Hz, C=CH; 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-t-Butyldimethylsilyloxymethylhept-2-en-1-yl)phenyl]trifluoroacetamide (15)

A stirred solution of (9) (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 t-butyllithium in pentane (2·0 M, 2 ml, 4 mmol). After stirring for 1 min, tetrakis[iodo(tributylphosphine)copper(I)][19] (0·75 g, 1·86 mmol) in anhydrous tetrahydrofuran (5 ml) was added, followed 5 min later by the allylic chloride (13) (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* (15) (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, $C=CCH_2$; 3·4, d, *J* 7 Hz, $ArCH_2C=C$; 4·1, s, CH_2O; 5·5, t, *J* 7 Hz, C=CH; 7·1–7·5, m, ArH; 7·8–8·3, m, ArH+NH. Mass spectrum (electron ionization) *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).

2-(3-Methoxymethylhept-2-en-1-yl)aniline (8)

The amide (11) (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 was extracted with dichloromethane (3×30 ml). The combined organic layers were dried over anhydrous sodium sulfate and evaporated to give a yellow oil which was microdistilled in a sublimator block to yield the *allylaniline* (8) (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). ^1H n.m.r. δ 0·7–1·6, br, $CH_2CH_2CH_3$; 2·2, m, $C=CCH_2$; 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=CH; 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).

Attempted Preparation of 2-Butyl-3-iodo-2-methoxymethyl-1,2,3,4-tetrahydroquinoline (19)

A mixture of the allylaniline (8) (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 atmosphere of nitrogen. The mixture was washed with aqueous, sodium thiosulfate

solution (10%, 8 ml) and the aqueous layer was extracted twice with dichloromethane. The combined organic layers were dried (sodium sulfate) and evaporated to give a brown, intractable oil. Attempts at chromatography only served to effect further decomposition.

Similar reactions carried out in darkness (reaction vessel covered with aluminium foil) and with 2 equiv. of iodine in darkness for either 4 or 1 h provided similar results. A reaction with 2 equiv. of iodine in darkness at 0° for 30 min returned starting material.

Attempted Synthesis of Amide (20) from (8)

A mixture of allylaniline (8) (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 was stirred for a further 1 h. The mixture was washed with aqueous sodium thiosulfate solution (10%, 10 ml) and the aqueous layer was 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 ^1H n.m.r. spectra were poorly resolved; (*c*) a pale, yellow oil corresponding by t.l.c. and ^1H n.m.r. spectroscopy to compound (4); and (*d*) a yellow oil whose infrared, ^1H 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-tetrahydroquinoline (21)

A solution of bromine in dichloromethane (1 M, 0·6 ml, 0·6 mmol) was added dropwise to a mixture of (8) (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 darkness at 0° for 30 min under nitrogen then washed with aqueous sodium thiosulfate 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). ^1H 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 (20) from (11)

A mixture of trifluoroacetamide (11) (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 thiosulfate solution (10%) and the aqueous layer was extracted twice with dichloromethane. The combined organic layers were dried and evaporated to yield unreacted (11).

A similar reaction, using saturated, aqueous sodium carbonate solution (4 ml) for 46 h, also returned starting material (11).

Ethyl 4-Amino-3-bromobenzoate (24)

This compound was prepared by the procedure of Leulier and Dinet,[20] m.p. 91–92° (lit.[20] 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 (25)

Trifluoroacetic anhydride (1·74 ml, 2·58 g, 12·29 mmol) was injected dropwise into a stirred solution of the amine (24) (2·00 g, 8·19 mmol) in dichloromethane (40 ml) at room temperature under an atmosphere of nitrogen. After stirring for 5 h, the mixture was washed with saturated, aqueous, sodium bicarbonate solution and the aqueous layer was extracted

[20] Leulier, A., and Dinet, J., *J. Pharm. Chim.*, 1928, **8**, 57 (*Chem. Abstr.*, 1929, **23**, 1892).

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* (25) (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 (26)

A stirred solution of (25) (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 t-butyllithium in pentane (2·0 M, 0·80 ml, 1·6 mmol). After stirring for 1 min, tetrakis[iodo(tributylphosphine)copper(I)][19] (0·30 g, 0·74 mmol) in anhydrous tetrahydrofuran (2 ml) was added, followed 5 min later by the allylic chloride (10) (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.

Acknowledgments

We thank the Australian Research Council Small Grants Scheme for partial support of this work. C.L.F. gratefully acknowledges an Australian Postgraduate Research Award.