Journal of Enzyme Inhibition and Medicinal Chemistry, 2002 Vol. 17 (3), pp. 137–154

Experiments Towards the Synthesis of the Ergot Alkaloids and Related Structures. Part 8.[17] The Total Synthesis of 4-Methyl-2,3,4,4a,5,6-hexahydro-benzo[*f*]quinoline-2-carbonitrile Hydrochloride Hemihydrate, an Immediate Precursor of the Despyrrole Analogues of Lysergic Acid and Its Amides

MARK A.E. BOWMAN[a], RALPH E. BOWMAN[a,*], ROY V. DAVIES[b], GERRY HARAN[b], PAUL J. HARRIS[b], H. JOHN SMITH[a], ROBERT W. STEELE[b], NIGEL WALKER[c] and KEITH WHITING[b]

[a]*Welsh School of Pharmacy, Cardiff University, Redwood Building, King Edward VII Avenue, Cardiff CF10 3XF, UK;* [b]*Knoll Limited, Pennyfoot Street, Nottingham NG1 1GF, UK;* [c]*BASF AG, Ludwigshafen, Germany*

(Received 1 February 2002)

Exposure of the *N*-methoxycarbonyl-bicyclic-keto-acid 5 **(improved preparation) to the Barnick β-keto-acid synthesis[1] yielded an aqueous solution of the sodium salts of the β-keto-acids** 26 **and** 27 **which on heating at 60–65°C furnished the *N*-methoxycarbonyl-tricyclic-ketone** 9 **(55%) plus the hydroxy-ketone** 28 **which on acid treatment raised the yield of** 9 **to 68%. Reduction ($NaBH_4$) of** 9 **yielded the alcohol** 32 **(94%) which was treated with thionyl chloride followed by copper (I) cyanide and sodium iodide in acetonitrile to give the tricyclic-*N*-methoxycarbonyl nitrile** 35 **whose relative configuration was obtained by X-ray analysis. Attempts to remove the *N*-methoxycarbonyl group from** 35 **were unsuccessful. Conversion of the alcohol** 32 **to its methoxypropyl ether** 41 **followed by reaction with ethereal MeLi–LiBr yielded the amino-alcohol** 39 **(75%) converted to the *N*-formyl-tricyclic alcohol** 42 **with formic-acetic anhydride (70%). The alcohol** 42 **was then converted into the *N*-formyl nitrile** 44 ***via* the chloride** 43 **as employed in the earlier synthesis of the nitrile** 35**. Removal of the *N*-formyl group from the nitrile** 44 **was achieved by refluxing methanolic hydrochloric acid to give the required amino-nitrile hydrochloride** 46 **(91%) whose structure was confirmed by X-ray analysis. Reaction of the free base with methyl iodide in ethyl acetate in the presence of calcium carbonate furnished the *N*-methyl base** 48 **isolated as its hydrochloride, hemihydrate** 49 **(59%). The overall yield of** 49 ***via* this eleven-step synthesis was 3.4%.**

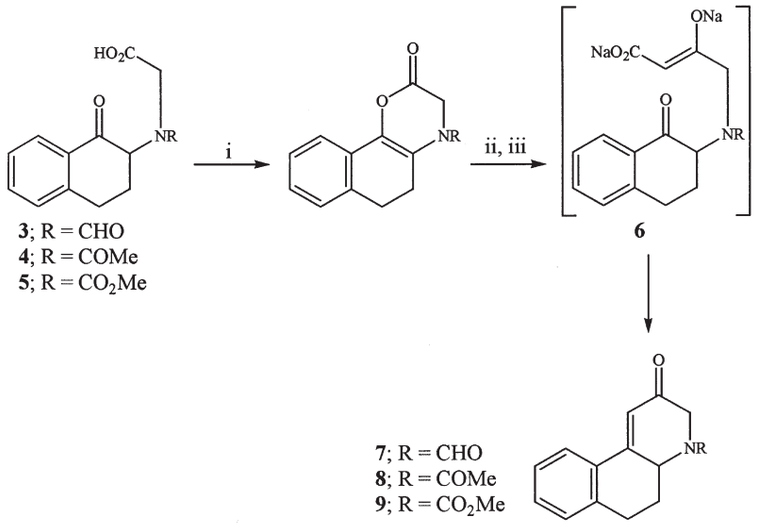
Keywords: Ergot alkaloids; Lysergic acid

INTRODUCTION

The medicinal application of the ergot alkaloids centres around the amidic (especially peptide) derivatives of lysergic acid. The epimeric iso-lysergic acid derivatives are biologically inert.[2] Since the introduction of the ergot alkaloids into established medicine, their pharmacological effects have been extensively investigated and include serotonin antagonism, vasoconstriction, oxytocic activity, psychotropic activity and inhibition of pituitary secretion of prolactin.[3,4] Isolation and structural elucidation of the pure ergot alkaloids was achieved in the early twentieth century by a number of independent research groups.[5,6] The desire to improve upon the potency of the natural alkaloids led Hofmann in 1943 to the discovery of LSD (lysergic acid diethyamide).[7] None of the many total synthetic routes to lysergic acid in the literature can offer a commercially viable alternative to the various cultivation methods which have been devised for the large-scale production of lysergic acid.[8–11] However,

*Corresponding author. Address: 15 Pencommin, Llangynidr, Crickhowell, Powys NP8 1LT, UK.

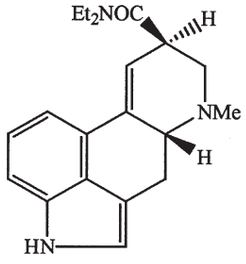
ISSN 1475-6366 print/ISSN 1475-6374 online © 2002 Taylor & Francis Ltd
DOI: 10.1080/14756360290032958



SCHEME 1 Reagents and conditions: i, Et_3N, Ac_2O, 95°C; ii, $KCH(CO_2SiMe_3)_2$, 60°C, iii, $NaHCO_3$, H_2O, 60–65°C.

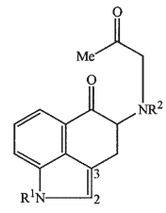
total synthesis does have the advantage of allowing various structural modifications to be introduced into the ergoline nucleus which are not found in nature. These modifications have led to the discovery of compounds with improved pharmacological profiles, *e.g.* bromoergocryptine.[12–14] The results of these studies have given drug design teams more detailed information about the features necessary for selective activity.

Here, the work led by Dr R.E. Bowman to instigate a long-term research programme aimed at devising a *novel*, *general* and *practical* synthesis of lysergic acid is pursued with des-pyrrole analogues.

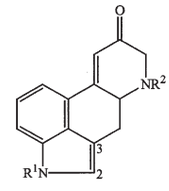


Lysergic acid diethylamide (LSD)

Progress[15] towards a novel general synthesis of lysergic acids capable of scale-up came to an abrupt halt when cyclisation of the des-pyrrole analogue *N*-methoxycarbonyl-tricyclic-diketone **1a** to the crucial tetracyclic monoketone **2a** under basic conditions failed despite the successful cyclisation of the related *N*-methylindoline-diketone **1b** to the corresponding tetracyclic ketone **2b** under the same conditions.[16] More recently, the cyclisation problem was solved in the model 1-tetralone series starting from the *N*-acyl-keto-acids **3**, **4** and **5** followed by cyclisation *via* the bis-sodium salts of the corresponding diketo-acids **6** to give the tricyclic-ketones **7**, **8** and **9** in 31–36% yield[17] (Scheme 1).



1a R^1=Ts, R^2=CO_2Me
1b (2,3-Dihydro) R^1=PhCO, R^2=Me



2a R^1=Ts, R^2=CO_2Me
2b (2,3-Dihydro) R^1=PhCO, R^2=Me

Although the above furnished the important intermediate tricyclic ketones **7**, **8** and **9**, the overall yields were unacceptably low due in the main to the poor yields obtained in the multi-stage preparations of the starting *N*-acyl-keto-acids from 1-tetralone[18,19] and the succeeding cyclisations outlined in Scheme 1.

Our first major target was the development of an improved synthesis capable of scale-up of the *N*-methoxycarbonyl-tricyclic-ketone **9**, chosen rather than the *N*-formyl **7** and the *N*-acetyl **8** analogues on account of the high stability of the *N*-methoxycarbonyl linkage.

EXPERIMENTAL

General Procedures

All melting points were determined on a Gallenkamp digital apparatus and are uncorrected. IR spectra were obtained as Nujol mulls, liquid films or

KBr discs using a Perkin–Elmer 681 instrument. ^{1}H-NMR spectra were recorded on either a Bruker AC 250 (250 MHz), a Bruker DPX 300 (300 MHz) or a Bruker AM 360 (360 MHz) spectrometer as dilute solutions in deuteriochloroform, unless stated otherwise, with tetramethylsilane as internal standard. Coupling constants, *J*, are reported in Hz. ^{13}C-NMR spectra were recorded as dilute solutions in deuteriochloroform unless stated otherwise on a Bruker AC 250 (62.9 MHz) instrument.

Merck silica gel 60 was used for flash chromatography and Merck silica gel 60 F_{254} precoated aluminium plates for thin layer chromatography (TLC). Solvents were dried using pre-activated 3 Å and 4 Å molecular sieves. Triethyl ammonium formate (TEAF) solution was prepared by addition of formic acid to a 0.1% solution of triethylamine in water to pH 3.5. Non-chiral chromatography was carried out using Spherisorb S5 C8 (Sph. C8) and Spherisorb S5 ODS-2 (SPh. ODS) columns (25 × 0.46 cm, Phase Separations Ltd, Deeside, Clwyd, U.K.) and chiral chromatography using Chiralcel OD (Chir. OD), Chiralcel OJ (Chir. OJ) and Chiralpak AS (Chir. AS) columns (25 × 0.46 cm, Daicel Chemical Industries Ltd, Japan). The chromatography results were reported as follows:

Column type; Mobile Phase (M.P.); Flow Rate (F.R.); Detection method (Det.); Retention Times (R.T.) with the percentages of the species detected being shown in brackets.

For the X-ray crystallographic studies, intensities were measured on a Siemens P4 diffractometer operating in the $\theta/2\theta$ mode using graphite-monochromated Cu-Kα radiation. Structures were solved by direct methods using SHELXS86.[20] Refinement was carried out using intensities, F_2, in SHELXL-93.[21] All hydrogen atoms were located on difference-Fourier syntheses and refined. The atomic coordinates, thermal parameters, and bond lengths and angles are available from the Cambridge Crystallographic Data Centre (CCDC deposition numbers 16289–16291).

2-Oxo-4-phenylbutanoic Acid (10)

Diethyl oxalate (99%; 81.5 cm^3, 0.6 mol) was added portionwise with stirring to an ice-water cooled suspension of potassium *tert*-butoxide (95%; 39 g, 0.33 mol) in anhydrous diethyl ether (700 cm^3). Ethyl 3-phenylpropionate (99%; 54 cm^3, 0.3 mol) was added in portions and the mixture stirred for 1 h at room temperature before being refluxed for 12 h. The cooled mixture was poured into ice-water (500 cm^3) and the aqueous layer isolated, washed with ethyl acetate (100 cm^3) and acidified with 1 mol dm^{-3} sulphuric acid. The aqueous layer was extracted with dichloromethane (2 × 200 cm^3) and the combined organic extracts washed with water (100 cm^3), dried ($MgSO_4$) and evaporated to give a brown oil. The oil was refluxed with sulphuric acid (2 mol dm^{-3}; 300 cm^3, 0.6 mol) and acetic acid (50 cm^3) for 12 h and the ethyl acetate produced removed by distillation through a 30 cm Vigreux column. On cooling, the organic layer was isolated and the aqueous layer extracted with dichloromethane (100 cm^3). The combined organic extracts were washed with water (100 cm^3), dried ($MgSO_4$) and evaporated to give a brown mobile liquid. Distillation gave the pure *keto-acid* **10** as a colourless mobile liquid (b.p. 130–131°C/0.5 mmHg) which solidified on standing (30 g, 56%), m.p. 44.5–45°C; ν_{max}(Nujol)/cm^{-1} 3450 (OH), 1740 (CO_2H), 1725 (C = O) and 1600 (Ar C = C); δ_H(300 MHz) 3.02 (2H, t, *J* 7.5, 4-H_2), 3.30 (2H, t, *J* 7.5, 3-H_2) and 7.24–7.42 (5H, m, Ar-H).

N-*Methoxycarbonyl-2-amino-4-phenylbut-2-enoic Acid (11)*

Methyl carbamate (98%; 8 g, 235 mmol) was added to a stirred suspension of the keto-acid **10** (40 g, 224 mmol) and toluene-*p*-sulphonic acid monohydrate (98%; 5 g, 26 mmol) in benzene (150 cm^3) (CARE-CARCINOGENIC). The mixture was refluxed for 4 h using a Dean–Stark separator (4.7 cm^3 of water was collected) and left overnight at room temperature. The mixture was evaporated and the semi-solid residue stirred with water (300 cm^3) for 10 min before being filtered and dried *in vacuo*. The resulting solid was stirred with diethyl ether (150 cm^3), filtered and dried *in vacuo*. Evaporation of the filtrates gave a viscous liquid which on trituration with ethyl acetate gave a second crop of the *carbamate-acid* **11** (combined yield 21.5 g, 41%). A pure sample (from ethyl acetate) had m.p. 174–175°C (Found: C, 61.23; H, 5.54; N, 5.97. $C_{12}H_{13}NO_4$ requires C, 61.27; H, 5.57; N, 5.96%); ν_{max} (KBr)/cm^{-1} 3289 (NH), 1720 (CO_2H), 1690 (carbamate) and 1600w (Ar C = C); δ_H(250 MHz; $(CD_3)_2SO$) 3.46 (2H, d, *J* 7.5, 4-H_2), 3.60 (3H, s, OCH_3), 6.48 (1H, td, *J* 7.5 and 0.8, 3-H), 7.18–7.34 (5H, m, Ar-H), 8.68 (1H, br s, NH) and 12.60 (1H, br s, CO_2H).

N-*Methoxycarbonyl-2-amino-4-phenylbutanoic Acid (12)*

A suspension of 10% palladium charcoal (4 g) and the unsaturated carbamate-acid **11** (15.8 g, 67 mmol) in propan-2-ol (150 cm^3) was shaken under an atmosphere of hydrogen for 1.5 h (total uptake 1570 cm^3; theory 1608 cm^3). After removal of the catalyst by filtration, evaporation of the filtrates gave the crude *carbamate-acid* **12** which was isolated by trituration with water, filtration and dried *in vacuo* (13.5 g, 85%), m.p. 106–108°C. A pure sample (from acetonitrile) had m.p. 110–111°C; ν_{max} (KBr)/cm^{-1}

3345 (NH), 1726 (CO_2H), 1694 (carbamate) and 1600w (Ar C = C); δ_H(250 MHz; $(CD_3)_2SO$) 1.79–2.04 (2H, m, 3-H_2), 2.53–2.74 (2H, m, 4-H_2), 3.56 (3H, s, OCH_3), 3.86–3.95 (1H, m, 2-H), 7.15–7.32 (5H, m, Ar-H), 7.57 (1H, d, *J* 8, NH) and 12.59 (1H, br s, CO_2H).

Methyl N-*Methoxycarbonyl-2-amino-4-phenylbutanoate (13)*

Trimethyl orthoformate (98%; 4.9 cm^3, 44 mmol) was added to a mixture of the carbamate-acid **12** (10 g, 42 mmol), sulphuric acid (96%; 0.2 cm^3) and anhydrous methanol (75 cm^3) and the mixture refluxed for 6 h. The mixture was kept at room temperature overnight, evaporated and the residue dissolved in dichloromethane (50 cm^3). The solution was washed with aqueous sodium hydrogen carbonate (1 mol dm^{-3}, 2 × 50 cm^3) and evaporated to give the crude *carbamate-ester* **13** as a viscous yellow liquid (9.5 g, 95%); ν_{max}(film)/cm^{-1} 3340 (NH), 1728 (CO_2Me), 1705 (carbamate) and 1600w (Ar C = C); δ_H(300 MHz) 1.96–2.09 (1H, m, 3-H), 2.17–2.28 (1H, m, 3-H), 2.73 (2H, t, *J* 7.8, 4-H_2), 3.74 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 4.43–4.50 (1H, m, 2-H), 5.58 (1H, d, *J* 7.9, NH) and 7.21–7.35 (5H, m, Ar-H).

N-*(1-Carboxy-3-phenylprop-1-yl)glycine (15) and 2-Hydroxy-4-phenylbutanoic Acid (16)*

The keto-acid **10** (3.6 g, 20 mmol) was added to a solution of glycine (98%; 1.5 g, 20 mmol) in aqueous sodium hydroxide (1 mol dm^{-3}; 40 cm^3, 40 mmol) and the mixture stirred for 0.5 h. The mixture was added to 10% palladium/charcoal (2 g) and shaken under an atmosphere of hydrogen for 1.5 h (total uptake 490 cm^3; theory 480 cm^3). The catalyst was removed by filtration and the alkaline solution neutralised with hydrochloric acid (2 mol dm^{-3}; 20 cm^3, 40 mmol). The crystalline *hydroxy-acid* **16** which precipitated was isolated by filtration, washed with water and dried *in vacuo* (800 mg, 22%), m.p. 102–104°C. A pure sample (from benzene) had m.p. 103–104°C; ν_{max}(KBr)/cm^{-1} 3460(OH), 1720 (CO_2H) and 1605 (Ar C = C); δ_H(300 MHz) 2.01–2.13 (1H, m, 3-H), 2.19–2.30 (1H, m, 3-H), 3.27 (2H, t, *J* 7.2, 4-H_2), 4.33 (1H, dd, *J* 7.9 and 4.0, 2-H), 5.92 (2H, br s, 2-OH and CO_2H) and 7.23–7.38 (5H, m, Ar-H). The filtrate was evaporated to half-volume and kept at 3°C for two days when the crude *amino-diacid* **15** was isolated by filtration, washed with water and dried *in vacuo* (3.1 g, 65%), m.p. 218–220°C (dec.). A pure sample (from 3:1 ethanol–water) had m.p. 218–220°C (dec.) (Found: C, 60.75; H, 6.4; N, 5.8. $C_{12}H_{15}NO_4$ requires C, 60.75; H, 6.3; N, 5.9%); ν_{max}(KBr)/cm^{-1} 3430 (OH), 1742 (CO_2H), 1605 (Ar C = C) and 1557 (CO_2^-); δ_H(250 MHz; $(CD_3)_2SO$) 1.95 (2H, m, 2-H_2), 2.56–2.79 (2H, m, 3-H_2), 3.40–3.54 (3H, m, 1-H and CH_2CO_2H) and 7.15–7.31 (5H, m, Ar-H).

N-*(1-Carboxy-3-phenylprop-1-yl)glycine Hemihydrochloride (20)*

(A) Preparation by Strecker-type Reaction

3-Phenylpropionaldehyde (95%; 68 cm^3, 490 mmol) was added in portions over 5 min to a stirred solution of sodium metabisulphite (97%; 48 g, 245 mmol) in water (150 cm^3) when a colourless crystalline complex began to separate. After the mixture had been stirred at room temperature for an additional 45 min, a solution of glycine (98%; 37.5 g, 490 mmol) and sodium hydroxide (97%, 20.2 g, 490 mmol) in water (70 cm^3) was added in one portion. The mixture was heated at 34°C for 30 min during which the majority of the crystalline complex entered solution. The reaction mixture was cooled to 20°C and potassium cyanide (97%; 32.9 g, 490 mmol) added in portions over 5 min. The resulting solution was stirred at room temperature for 2.5 h when hydrochloric acid (12 mol dm^{-3}; 480 cm^3, 5.76 mol) was added in portions over 5 min and a colourless solid began to separate. The reaction mixture was heated at 106°C for 7 h and stirred overnight at room temperature. The resulting solid, contaminated with a dark viscous oil, was filtered and dried *in vacuo* over a period of several days. Following repeated trituration of the solid with acetone–diethyl ether (1:1), the crude *hemihydrochloride* **20** was isolated by filtration and dried *in vacuo* (113.3 g, 91%), m.p. 225–226°C (dec.). A pure sample (from 4 mol dm^{-3} hydrochloric acid) had m.p. 224–226°C (dec.) (Found: C, 56.35; H, 6.1; N, 5.3; ionic Cl, 7.3. $C_{12}H_{15}NO_4$. 0.5 HCl requires C, 56.40; H, 6.1; N, 5.5; ionic Cl, 7.0%); ν_{max}(KBr)/cm^{-1} 3409 (OH), 1769 (CO_2H), 1725 (CO_2H) and 1600w (Ar C = C); δ_H(250 MHz; $(CD_3)_2SO$) 1.98–2.14 (2H, m, 2-H_2), 2.56–2.84(2H, m, 3-H_2), 3.64–3.78 (3H, m, 1-H and CH_2CO_2H), 7.16–7.33 (5H, m, Ar-H) and 9.49 (2H, br s, 2 × CO_2H).

(B) Preparation from (**15**)

A sample of the amino-diacid **15** was recrystallised from 6 mol dm^{-3} hydrochloric acid to give the pure *hemihydrochloride* **20**, m.p. and mixed m.p. (with an authentic sample prepared using the above method) 225–226°C (dec.).

N-*Methoxycarbonyl*-N-*(1-carboxy-3-phenylprop-1-yl)glycine (21)*

Sodium hydrogen carbonate (99%; 27.2 g, 0.32 mol) was added in portions to a vigorously stirred ice-water cooled suspension of the hemihydrochloride **20** (40.6 g, 0.16 mol) in water (500 cm^3). Methyl chloroformate (99%; 25 cm^3, 0.32 mol) and sodium hydrogen carbonate (99%; 41 g, 0.48 mol) were simultaneously added in portions over 1.5 h to the resulting mixture, at 3°C. The mixture was stirred for an additional 1.5 h before hydrochloric acid

($12\,mol\,dm^{-3}$; $100\,cm^3$) was added in portions over 10 min resulting in the separation of a colourless oil. The mixture was left overnight at room temperature when a solid was deposited. The aqueous solution was decanted and the solid, washed with water ($20\,cm^3$) and dried *in vacuo*. Trituration of the solid with ethyl acetate ($20\,cm^3$), filtration and dried *in vacuo* gave the crude *carbamate-diacid* **21**. The aqueous solution was extracted with ethyl acetate ($2 \times 200\,cm^3$) and the combined organic layers washed with water ($100\,cm^3$), dried ($MgSO_4$) and evaporated to give a colourless viscous liquid which spontaneously crystallised on standing to give a second crop (total yield 42.6 g, 90%), m.p. 151–153°C. A pure sample (from ethyl acetate) had m.p. 155–157°C (Found: C, 57.15; H, 5.8; N, 4.8. $C_{14}H_{17}NO_6$ requires C, 56.9; H, 5.8; N, 4.7%); ν_{max}(KBr)/cm^{-1} 3400 (OH), 1765 (CO_2H), 1720 (CO_2H), 1660 (carbamate) and 1606w (Ar C = C); δ_H(360 MHz; $(CD_3)_2SO$) 1.85–2.02 (1H, m, 2-H), 2.04–2.19 (1H, m, 2-H), 2.54–2.71 (1H, m, 3-H), 2.76–2.88 (1H, m, 3-H), 3.10–3.55 (1H, br, CO_2H), 3.59 and 3.61 (3H, 2 × s, OCH_3), 3.82 (1/3H, d, *J* 4.9, 1/3 × CH_2CO_2H), 3.87 (2/3H, d, *J* 5.6, 2/3 × CH_2CO_2H), 3.94 (2/3H, d, *J* 9.0, 2/3 × CH_2CO_2H), 3.99 (1/3H, d, *J* 9.5, 1/3 × CH_2CO_2H), 4.43 (1/3H, dd, *J* 4.9 and 9.7, 1/3 × 1-H), 4.59 (2/3H, dd, *J* 4.8 and 9.8, 2/3 × 1-H), 7.12–7.42 (5H, m, Ar-H) and 12.45–13.05 (1H, br, CO_2H).

The complexity of the spectrum reported above was assumed to be caused by restriction of rotation about the C–NCO_2Me bond. In order to test this theory, the compound's spectrum was re-recorded at 95°C when a much simpler spectrum was obtained; δ_H(360 MHz; $(CD_3)_2SO$; performed at 95°C) 1.93–2.02 (1H, m, 2-H), 2.08–2.18 (1H, m, 2-H), 2.61–2.69 (1H, m, 3-H), 2.74–2.82 (1H, m, 3-H), 3.61 (3H, s, OCH_3), 3.82 (1H, d, *J* 17.8, CH_2CO_2H), 3.99 (1H, d, *J* 17.8, CH_2CO_2H), 4.49 (1H, br s, 1-H) and 7.13–7.28 (5H, m, Ar-H).

N-*Methoxycarbonyl-N-(1,2,3,4-tetrahydro-1-oxo-2-naphthyl)glycine (5)*

Trifluoroacetic anhydride (99%; $59\,cm^3$, 0.4 mol) was added to a vigorously stirred suspension of the carbamate-diacid **21** (59.1 g, 0.2 mol) in dichloroethane ($500\,cm^3$). The mixture was stirred for 1 h, evaporated and the residue dissolved in dichloromethane ($200\,cm^3$). Aluminium chloride (98%; 88 g, 0.65 mol) was added in portions to the stirred solution, at −15°C under nitrogen. The mixture was stirred for 5 h at 3°C before being added in portions to a vigorously stirred mixture of hydrochloric acid ($12\,mol\,dm^{-3}$; $80\,cm^3$, 0.96 mol) and ice-water ($100\,cm^3$). After standing overnight at room temperature, the cloudy organic layer was evaporated and the remaining water removed by decantation. The residue was re-dissolved in dichloromethane ($200\,cm^3$), charcoal added and filtered through Celite. The filtrate was evaporated to give a viscous oil which was treated with boiling diethyl ether ($200\,cm^3$). The ethereal solution was decanted from the insoluble material and cooled to 3°C to give the crude *carbamate-acid* **5** which was isolated by filtration, washed with diethyl ether and dried *in vacuo* (33.1 g, 60%), m.p. 140–142°C. A pure sample (from benzene), had m.p. 142–144°C.

Methyl 2-Oxo-2,3,4,4a,5,6-hexahydrohenzo[f]-quinoline-4-carboxylate (9) and Methyl 10b-Hydroxy-2-oxo-1,2,3,4,4a,5,6,10b-octahydro-benzo[f]quinoline-4-carboxylate (28)

n-Butyl lithium ($1.6\,mol\,dm^{-3}$ solution in hexanes; $72.5\,cm^3$, 116 mmol) was added dropwise over 1 h to a stirred solution of bis-(trimethylsilyl) malonate (98%; $30.2\,cm^3$, 116 mmol) in anhydrous diethyl ether ($300\,cm^3$), at −78°C under nitrogen. Simultaneously, oxalyl chloride (98%; $10.3\,cm^3$, 116 mmol) and dimethylformamide (2 drops) were added to a stirred suspension of the carbamate-acid **5** (16.1 g, 58 mmol) in benzene ($100\,cm^3$) (CARE-CARCINOGEN). After 1 h, the resulting solution was evaporated (<40°C) and the residue re-evaporated with toluene ($75\,cm^3$) under a high-vacuum (<40°C). The residue was dissolved in benzene ($100\,cm^3$) and the solution added dropwise over 1 h to the stirred solution of bis(trimethylsilyl) lithio malonate, at −78°C under nitrogen. The mixture was allowed to come to room temperature before being poured into a vigorously stirred mixture of sodium hydrogen carbonate (99%; 24 g, 0.28 mol) and ice-water ($200\,cm^3$). The organic layer was extracted with water ($100\,cm^3$) and the combined aqueous extracts washed with diethyl ether ($100\,cm^3$) before being evaporated to remove any diethyl ether. The resulting solution was heated at 60°C for 0.5 h when the product separated as a viscous oil. The mixture was stirred with dichloromethane ($100\,cm^3$) and the aqueous layer re-extracted with dichloromethane ($2 \times 50\,cm^3$). The combined organic extracts were washed with water ($100\,cm^3$), dried ($MgSO_4$), treated with charcoal, filtered through Celite and evaporated to give a viscous oil, which on treatment with boiling methanol ($75\,cm^3$) solidified. The crude *carbamate-ketone* **9** was isolated by filtration, washed with diethyl ether and dried *in vacuo* (7.8 g, 55%), m.p. 124–126°C. A pure sample (from methanol) had m.p. 126–127°C; Chir. OJ, M.P. n-C_6H_{12}:EtOH (75:25), F.R. $0.5\,cm^3\,min^{-1}$, Det. UV 288 nm, R.T. 27.13 min (49.9%) and 32.23 min (50%) (Found: C, 69.8; H, 5.9; N, 5.5. $C_{15}H_{15}NO_3$ requires C, 70.0; H, 5.8; N, 5.4%); ν_{max}(KBr)/cm^{-1} 1693 (carbamate), 1666 (conj. C = O), 1617 (conj. C = C) and 1598 (Ar C = C); δ_H(250 MHz) 2.09

(1H, qd, *J* 12.3 and 6, 5-H), 2.34–2.42 (1H, m, 5-H), 3.08 (1H, dd, *J*, 17.5 and 5.5, 6-H), 3.19–3.33 (1H, m, 6-H), 3.73 (1H, d, *J* 17.7, 3-H), 3.79 (3H, s, OMe), 4.62 (1H, d, *J* 18, 3-H), 4.91 (1H, dd, *J* 13.2 and 2, 4a-H), 6.46 (1H, d, *J* 1.7, 1-H), 7.18–7.29 (2H, m, 7,9-H), 7.37 (1H, td, *J* 7.5 and 1.5, 8-H) and 7.55 (1H, dd, *J* 6.8 and 1.3, 10-H). The methanolic mother liquors were evaporated and the residue (3.3 g) subjected to flash chromatography on silica–gel (2:1 diethyl ether–petroleum). Evaporation of the relevant fractions and treatment of the residue with diethyl ether gave the *hydroxy-ketone* **28** which was isolated by filtration, washed with diethyl ether and dried *in vacuo* (210 mg), m.p. 149.5–152.5°C (Found: C, 65.45; H, 6.2; N, 5.0. $C_{15}H_{17}NO_4$ requires C, 65.45; H, 6.2; N, 5.1%); ν_{max}(KBr)/cm^{-1} 3467 (OH), 1729 (C = O), 1682 (carbamate) and 1600 (Ar C = C). δ_H(250 MHz) 2.07–2.18 (2H, m, 5-H_2), 2.56–3.20 (5H, m, 1-H_2, 6-H_2 and 10b-H), 3.60–3.78 (4H, m, OCH_3 and 4a-H), 4.37–4.52 (2H, m, 3-H_2), 7.08–7.11 (1H, m, 7-H), 7.18–7.26 (2H, m, 8,9-H) and 7.55–7.57 (1H, m, 10-H). The hydroxy-ketone **28** (100 mg) was suspended in benzene (10 cm^3) (CARE-CARCINOGENIC), toluene-*p*-sulphonic acid monohydrate (98%, 5 mg) added and the mixture refluxed for 0.5 h. The resulting solution was evaporated and the residue dissolved in dichloromethane (10 cm^3). The solution was washed with saturated aqueous sodium hydrogen carbonate (10 cm^3) and water (10 cm^3), evaporated and the residue treated with methanol to give the crude *carbamate-ketone* **9**, m.p. and mixed m.p. (with an authentic sample) 124–126°C.

In a separate experiment, the residue obtained from evaporation of the methanolic mother liquors (3.4 g) was dissolved in benzene (30 cm^3), toluene-*p*-sulphonic acid monohydrate (98%, 300 mg) added and the mixture refluxed for 1 h using a Dean–Stark separator. The resulting solution was evaporated and the residue dissolved in dichloromethane (50 cm^3). The solution was washed with saturated aqueous sodium hydrogen carbonate (50 cm^3) and water (50 cm^3), dried ($MgSO_4$), treated with charcoal and filtered through Celite. The filtrates were evaporated and the residue treated with boiling methanol (10 cm^3) to give a second crop of the *carbamate-ketone* **9** (1.6 g), m.p. and mixed m.p. (with an authentic sample) 124–126°C. In this way, the combined yield of **9** was raised to 68%.

Methyl 2-Hydroxyimino-2,3,4,4a,5,6-hexahydrobenzo[f]quinoline-4-carboxylate (30)

Hydroxylamine hydrochloride (99%; 1.5 g, 21 mmol) was added to a suspension of the carbamate-ketone **9** (1.3 g, 5 mmol) in ethanol–water (2:1; 45 cm^3) and the mixture warmed to 40°C. Potassium carbonate (99%; 1.4 g, 10 mmol) was added in portions and the mixture refluxed for 2 h. The ethanol present was removed by evaporation and the crude *oxime* **30** isolated by filtration, washed with water and dried *in vacuo* (1.3 g, 95%), m.p. 204–206°C. A pure sample (from methanol) had m.p. 206–207°C (Found: C, 66.1; H, 5.9; N, 10.1. $C_{15}H_{16}N_2O_3$ requires C, 66.2; H, 5.9; N, 10.3%); ν_{max}(KBr)/cm^{-1} 3316 (OH), 1678 (carbamate) and 1633 (conj. C = C); δ_H(360 MHz; $(CD_3)_2SO$) 1.91–1.96 (1H, m, 5-H), 2.08–2.17 (1H, m, 5-H), 2.96–3.07 (2H, m, 6-H_2), 3.60 (1H, d, *J* 17.3, 3-H), 3.68 (3H, s, OCH_3), 4.57 (1H, d, *J* 11.7, 4a-H), 5.18 (1H, d, *J* 17.2, 3-H), 6.59 (1H, d, *J* 1.7, 1-H), 7.11–7.30 (3H, m, 7,8,9-H), 7.64 (1H, d, *J* 6.6, 10-H) and 11.32 (1H, s, OH).

Methyl 2,2-Ethylenedioxy-1,2,3,4,5,6,-hexahydrobenzo[f]quinoline-4-carboxylate (31)

Boron trifluoride diethyl etherate (1.2 cm^3,10 mmol) was added to a solution of the carbamate-ketone **9** (260 mg, 1 mmol) and ethylene glycol (99%; 1.2 cm^3, 22 mmol) in dichloromethane (20 cm^3). After vigorous stirring at room temperature for 24 h, the mixture was diluted with water (10 cm^3) and the organic layer washed with saturated aqueous sodium hydrogen carbonate (10 cm^3), dried ($MgSO_4$) and evaporated to give the crude *ketal* **31** (200 mg, 66%), m.p. 95–100°C. A pure sample (from ethanol) had m.p. 102–103°C (Found: C, 67.74; H, 6.42; N, 4.57. $C_{17}H_{19}NO_4$ requires C, 67.76; H, 6.35, N, 4.65%); ν_{max}(Nujol)/cm^{-1} 1710 (carbamate) and 1634 (conj. C = C); δ_H(300 MHz) 2.68–2.72 (2H, m, 5-H_2), 2.75 (2H, s, 1-H_2), 2.85–2.94 (2H, m, 6-H_2), 3.68 (2H, s, 3-H_2), 3.82 (3H, s, OCH_3), 4.10–4.18 (4H, m, 2′-H_2 and 3′-H_2) and 7.12–7.25 (4H, m, 7,8,9,10-H).

Methyl 2-Hydroxy-2,3,4,4a,5,6-hexahydrobenzo[f]quinoline-4-carboxylate (32)

Sodium borohydride (99%; 5.5 g, 144 mmol) was added in portions over 10 min to a stirred suspension of the carbamate-ketone **9** (33.3 g, 129 mmol) in ethanol–water (8:1; 450 cm^3). The resulting solution was stirred at room temperature for 0.5 h, decanted from a small quantity of insoluble material and acidified with hydrochloric acid (2 mol dm^{-3}; 100 cm^3). The resulting solution was evaporated to remove the ethanol present and extracted with dichloromethane (2 × 50 cm^3). The combined organic extracts were washed with water (50 cm^3), dried ($MgSO_4$) and evaporated. The residue was triturated with diethyl ether (50 cm^3) and the crude *carbamate-alcohol* **32** isolated by filtration and dried *in vacuo* (31.3 g, 94%), m.p. 144–146°C. A pure sample (from methanol) had m.p. 147–148°C; Sph. ODS, M.P. MeOH:H_2O (60:40), F.R. 1.0 cm^3 min^{-1}, R.T. 11.48 min (99.4%) and 19.40 min (0.6%); Chir. OD, M.P. iso-hexane:2-propanol (80:20), F.R. 0.5 cm^3 min^{-1}, R.T. 11.03 min (0.2%), 13.20 min (0.2%), 21.72 min (50.0%) and 29.57 min (49.7%)

(Found: C, 69.4; H, 6.5; N, 5.35. $C_{15}H_{17}NO_3$ requires C, 69.5; H, 6.6; N, 5.4%); ν_{max}(KBr)/cm^{-1} 3473 (OH), 1681 (carbamate) and 1600sh (Ar C = C); δ_H(250 MHz) 1.91 (1H, qd, *J* 12.5 and 6, 5-H), 2.13–2.18 (1H, m, 5-H), 2.61–2.71 (2H, m, 3-H and 2-OH), 2.95 (1H, dd, *J* 17.5 and 6, 6-H), 3.11 (1H, ddd, *J* 18, 12 and 6, 6-H), 3.74 (3H, s, OCH_3), 4.41–4.50 (3H, m, 2-H, 3-H, and 4a-H), 6.16 (1H, s, 1-H), 7.05–7.25 (3H, m, 7,8,9-H) and 7.47 (1H, dd, *J* 7.5 and 1.5, 10-H); δ_C(62.9 MHz) 28.3 (5-CH_2), 28.8 (6-CH_2), 44.3 (3-CH_2), 52.1 (4a-CH), 52.8 (OCH_3), 65.0 (2-CH), 123.9 (1-CH), 124.0 (10-CH), 126.1, 127.9 and 128.9 (7,8,9-CH), 133.9, 135.2 and 136.3 (6a, 10a, 10b-C) and 155.6 (CO_2Me).

4-Methyl-2,3,4,4a,5,6-hexahydrobenzo[f]quinolin-2-ol (33)

Diisobutylaluminium hydride (1 mol dm^{-3} solution in dichloromethane; 20 cm^3) was added dropwise with stirring to an ice-water cooled solution of the carbamate-ketone **9** (1 g, 4 mmol) in dichloromethane (30 cm^3). The mixture was stirred at room temperature for 3 h before excess aqueous sodium hydroxide solution (1 mol dm^{-3}) was added dropwise. The resulting gelatinous mixture was filtered through Celite and the organic layer extracted with hydrochloric acid (1 mol dm^{-3}; 2 × 20 cm^3). The aqueous extracts were basified with aqueous ammonia (d = 0.880) and the resulting mixture extracted with dichloromethane (2 × 25 cm^3). The combined organic extracts were washed with water (50 cm^3), dried ($MgSO_4$) and evaporated. The residue was triturated with diethyl ether (5 cm^3) and the crude *amino-alcohol* **33** isolated by filtration and dried *in vacuo* (500 mg, 58%), m.p. 141–143°C. A pure sample (from diethyl ether–methanol) had m.p. 144–145°C (Found: C, 78.0, H, 7.9; N, 6.4. $C_{14}H_{17}NO$ requires C, 78.1; H, 8.0; N, 6.5%); ν_{max}(Nujol)/cm^{-1} 3180 (OH), 1640 (conj. C = C) and 1600w (Ar C = C); δ_H(300 MHz; $(CD_3)_2SO$) 1.46 (1H, qd, *J* 11.8 and 5.0, 5-H), 2.34–2.41 (4H, m, 5-H and N-CH_3), 2.61 (1H, dd, *J* 10.6 and 1.6, 6-H), 2.75–2.87 (3H, m, 2-OH, 3-H and 6-H), 3.38 (1H, br s, 3-H), 4.04 (1H, br s, 2-H), 4.73 (1H, d, *J* 6.9, 4a-H), 6.32 (1H, d, *J* 4.6, 1-H), 7.10–7.21 (3H, m, 7,8,9-H) and 7.57–7.64 (1H, m, 10-H).

Methyl 2-Chloro-2,3,4,4a,5,6-hexahydrobenzo[f]quinoline-4-carboxylate (34)

Thionyl chloride (97%; 0.15 cm^3, 2 mmol) was added to a stirred solution of the carbamate-alcohol **32** (259 mg, 1 mmol) in dichloromethane (10 cm^3). The mixture was stirred for 0.5 h and evaporated (< 40°C) to give a viscous oil. The latter was dissolved in toluene (10 cm^3) and the solution evaporated under vacuum (< 40°C) to give the *chloride* **34** as a yellow viscous oil (270 mg, 97%); ν_{max}(film)/cm^{-1} 1710–1690 (carbamate, mixture of α- and β-epimers), 1640 (conj. C = C) and 1600w (Ar C = C); δ_H(300 MHz) 1.94–2.12 (1H, m, 5-H), 2.17–2.28 (1H, m, 5-H), 2.97–3.28 (3H, m, 3-H and 6-H_2), 3.83–3.86 (3H, 2 × s, ratio 2:1, mixture of α- and β-epimers, OCH_3), 4.49–4.79 (3H, m, 2-H, 3-H and 4a-H), 6.27 and 6.40 (1H, br s and br d, ratio 2:1, *J* 5.2, 1-H), 7.17–7.34 (3H, m, 7,8,9-H) and 7.51–7.58 (1H, m, 10-H).

Methyl 2-Cyano-2,3,4,4a,5,6-hexahydrobenzo[f]quinoline-4-carboxylate (35)

Sodium iodide (99%; 7.6 g, 50 mmol) was dried *in vacuo* at 80°C for 1 h before being dissolved in acetonitrile (50 cm^3). Simultaneously, thionyl chloride (97%, 3.8 cm^3, 50 mmol) was added to a stirred solution of the carbamate-alcohol **32** (6.5 g, 25 mmol) in dichloromethane (50 cm^3). The mixture was stirred for 0.5 h and evaporated (< 40°C) to give the *chloride* **34** as a viscous oil (ν_{max}(film)/cm^{-1} 1710–1690 (carbamate, mixture of α- and β-epimers), 1640 (conj. C = C) and 1600w (Ar C = C)). The latter was dissolved in toluene (50 cm^3) and the solution evaporated under a high-vacuum (< 40°C). The resulting oil was dissolved in acetonitrile (50 cm^3) and the solution added with stirring to the solution of sodium iodide in acetonitrile. Copper (I) cyanide (99%, 13.6 g, 150 mmol) was added to the mixture and the resulting slurry stirred overnight at room temperature. The mixture was diluted with benzene (100 cm^3) and stirred for 10 min before being filtered through a thick pad of Celite. The combined filtrates were washed with freshly prepared aqueous sodium thiosulphate solution (0.2 mol dm^{-3}; 2 × 100 cm^3) and water (50 cm^3). The organic layer was evaporated and the residue treated with boiling dichloromethane (100 cm^3), dried ($MgSO_4$), treated with charcoal and filtered through Celite. The filtrates were evaporated and the solid residue triturated with diethyl ether (20 cm^3). The crude of *carbamate-nitrile* **35** was isolated by filtration, washed with diethyl ether and dried *in vacuo* (4.6 g, 70%) m.p. 166–168°C. A pure sample (from much methanol) had m.p. 174.5–175°C (Found: C, 71.3; H, 6.0; N, 10.4. $C_{16}H_{16}N_2O_2$ requires C, 71.6; H, 6.0; N, 10.4%); ν_{max}(KBr)/cm^{-1} 2240 (CN), 1690 (carbamate), 1649 (conj. C = C) and 1605w(Ar C = C); δ_H(250 MHz) 1.92 (1H, qd, *J* 12.5 and 5, 5-H), 2.17–2.22 (1H, m, 5-H), 2.99 (1H, dd, *J* 16 and 5.6, 6-H), 3.07–3.23 (2H, m, 3-H and 6-H), 3.41–3.45 (1H, m, 2-H), 3.80 (3H, s, OCH_3), 4.57 (1H, d, *J* 13.3, 3-H), 4.71 (1H, d, *J* 12.8, 4a-H) 6.15 (1H, d, *J* 7, 1-H), 7.10–7.28 (3H, m, 7,8,9-H) and 7.48 (1H, dd, *J* 7.6 and 1.6, 10-H); δ_C(62.9 MHz) 27.1 (2-CH), 28.3 (5-CH_2), 28.6 (6-CH_2), 39.8 (3-CH_2), 52.2 (4a-CH), 53.1 (OCH_3), 111.4 (1-CH), 118.5 (2-CN), 124.1 (10-CH), 126.4, 128.8 and 129.1 (7,8,9-CH), 133.1, 135.5 and 140.7 (6a, 10a, 10b-C) and 155.4 (CO_2Me).

Methyl 2-Aminocarbonyl-2,3,4,4a,5,6-hexahydrobenzo[f]quinoline-4-carboxylate (36)

An ice-water cooled solution of the carbamate-nitrile **35** (1 g, 3.7 mmol) in acetone (100 cm^3) was treated with hydrogen peroxide solution (30 wt%; 10 cm^3). The dark orange mixture was treated with aqueous sodium hydroxide solution (2 mol dm^{-3}; 4 cm^3) when a dark oil precipitated. After stirring for 20 min, a second portion of hydrogen peroxide solution (10 cm^3) in acetone (50 cm^3) was added and stirring continued for 40 min during which the oily precipitate gradually hardened. The aqueous portion was decanted and the semi-solid residue dissolved in water (100 cm^3). The solution was extracted with ethyl acetate (2 × 50 cm^3) and the combined aqueous portions heated at 40°C for 2 h before being stood overnight at room temperature. The mixture was diluted with water (100 cm^3) and evaporated to remove any remaining acetone. The crude *amide* **36** which precipitated was isolated by filtration, washed with water and dried *in vacuo* (380 mg). The filtrates were extracted with ethyl acetate (2 × 75 cm^3) and the combined organic layers dried ($MgSO_4$) and evaporated to yield a gum which on trituration with methanol and ice-water cooling gave a second crop (total yield 580 mg, 55%) m.p. 177–185°C. A pure sample (from methanol) had m.p. 216–217°C (Found: C, 66.7; H, 6.3; N, 9.7. $C_{16}H_{18}N_2O_3$ requires C, 67.1; H, 6.3; N, 9.8%); ν_{max}(Nujol)/cm^{-1} 3400 and 3210 ($CONH_2$), 1690 (carbamate), 1660 ($CONH_2$), 1620 (conj. C = C) and 1600 (Ar C = C); δ_H (300 MHz; $(CD_3)_2SO$) 1.87–1.91 (1H, m, 5-H), 2.01–2.04 (1H, m, 5-H), 2.85–3.02 (3H, m, 3-H and 6-H_2), 3.13–3.18 (1H, m, 2-H), 3.63 (3H, s, OCH_3), 4.24 (1H, d, *J* 9, 3-H), 4.40 (1H, d, *J* 10.4, 4a-H), 6.27 (1H, s, 1-H), 7.11–7.22 (4H, m, 7,8,9,10-H) and 7.52–7.66 (2H, m, $CONH_2$).

2,3,4,4a,5,6-Hexahydrobenzo[f]quinolin-2-ol 39 and 4-Acetyl-2,3,-4,4a,5,6-hexahydrobenzo[f]quinolin-2-ol (40)

Methyllithium–lithium bromide complex (1.5 mol dm^{-3} solution in diethyl ether; 50 cm^3, 75 mmol) was added in portions over a period of 5 min to an ice-water cooled suspension of the carbamate–alcohol **32** (2.6 g, 10 mmol) in dry diethyl ether (50 cm^3). The resulting mixture was refluxed for 1.5 h, cooled and water (30 cm^3) carefully added over a period of 5 min. The organic layer was extracted with hydrochloric acid (1 mol dm^{-3}; 2 × 40 cm^3), dried ($MgSO_4$) and evaporated to yield a dark oil. The latter was triturated with a small volume of ice-cold diethyl ether to give the crude *acetamido-alcohol* **40** (500 mg, 21%), m.p. 177–179°C. A pure sample (from ethanol) had m.p. 202–203°C (Found: C, 74.15; H, 7.1; N, 5.65. $C_{15}H_{17}NO_2$ requires C, 74.05; H, 7.0; N, 5.8%); ν_{max}(Nujol)/cm^{-1} 3349br (OH) and 1605br (3° amide and Ar C = C); δ_H(300 MHz; $(CD_3)_2SO$) 1.81 (1H, qd, *J* 12.1 and 6.4, 5-H) 1.96–2.08 (1H, m, 5-H), 2.10 and 2.11 (3H, 2 × s, ratio 1:1, OCH_3), 2.31 (1/2H, dd, *J* 12.6 and 9.9, 1/2 × 3-H), 2.80 (1/2H, dd, *J* 12.6 and 9.9, 1/2 × 3-H), 2.89–3.20 (2H, m, 6-H), 3.92 (1/2H, dd, *J* 12.7 and 5.9, 1/2 × 3-H), 4.09 (1/2H, dd, *J* 12.7 and 5.9, 1/2 × 3-H), 4.24–4.36 (1H, m, 2-H), 4.60–4.70 (1H, m, 4a-H), 5.32 (1H, d, *J* 8.9, 2-OH), 6.17 (1H, br s, 1-H), 7.12–7.23 (3H, m, 7,8,9-H) and 7.52–7.58 (1H, m, 10-H). The acidic extracts from above were stirred at room temperature for 0.5 h before being made alkaline with aqueous ammonia (d = 0.880). The resulting oil was extracted with dichloromethane (2 × 50 cm^3) and the combined organic extracts washed with water (50 cm^3) and evaporated. The residue was triturated with ice-cold diethyl ether to give the crude *amino-alcohol* **39** (750 mg, 37%), m.p. 129–132°C. A pure sample (from ethyl acetate) had m.p. 133–134°C; Sph. C8, M.P.MeCN:TEAF (20:80), F.R. 2.0 cm^3 min^{-1}, Det. UV 212 nm, R.T. 4.60 min (99.2%) and 14.05 min (0.8%); Chir. OD, M.P. iso-hexane: EtOH (75:25), F.R. 0.5 cm^3 min^{-1}, Det. UV 212 nm, R.T. 10.95 min (0.3%), 13.27 min (51.0%) and 22.37 min (48.7%) (Found: C, 77.6; H, 7.5; N, 6.8. $C_{13}H_{15}NO$ requires C, 77.6, H, 7.5; N, 7.0%); ν_{max}(Nujol)/cm^{-1} 3306 (OH); δ_H(300 MHz; $(CD_3)_2SO$) 1.55 (1H, qd, *J* 12.2 and 6.1, 5-H), 1.99–2.06 (1H, m, 5-H), 2.48–2.92 (5H, m, 2-H, 3-H, 6-H_2 and NH), 3.22 (1H, dt, *J* 12.4 and 1.8, 3-H), 3.92 (1H, d, *J* 1.7, 4a-H), 6.34 (1H, d, *J* 4.6, 1-H), 7.08–7.19 (3H, m, 7,8,9-H) and 7.60–7.64 (1H, m, 10-H).

2,3,4,4a,5,6-Hexahydrobenzo[f]quinolin-2-ol (39)

Toluene-4-sulphonic acid monohydrate (98%; 50 mg, 0.3 mmol) was added with stirring to an ice-water cooled suspension of the carbamate-alcohol **32** (16 g, 62 mmol) in dry diethyl ether (400 cm^3). 2-Methoxypropene (97%; 8 cm^3, 81 mmol) was added and stirring continued for 0.5 h to give a clear solution of the corresponding ether. Methyllithium–lithium bromide complex (1.5 mol dm^{-3} solution in diethyl ether; 160 cm^3, 240 mmol) was added in portions over a period of 5 min resulting in the formation of a fine colourless precipitate. The mixture was refluxed for 1.5 h, cooled and water (100 cm^3) carefully added over a period of 5 min. The organic layer was separated, extracted with hydrochloric acid (1 mol dm^{-3}; 2 × 100 cm^3) and the acidic extracts stirred at room temperature for 0.5 h before being made alkaline with aqueous ammonia (d = 0.880; 40 cm^3). The resulting oil was extracted with dichloromethane (2 × 100 cm^3) and the combined organic extracts washed with water (100 cm^3) and evaporated. The residue was triturated with ice-cold diethyl ether (20 cm^3) to give the crude *amino-alcohol* **39** (9.4 g, 75%), m.p. 129–132°C. A pure sample

(from ethyl acetate) had m.p. and mixed m.p. (with an authentic sample) 133–134°C.

4-Formyl-2,3,4,4a,5,6-hexahydrobenzo[f]quinolin-2-ol (42)

A stirred mixture of acetic anhydride (98%; 16 cm^3, 0.2 mol) and formic acid (96%; 40 cm^3, 1 mol) was heated at 50°C for 15 min. On cooling, the amino-alcohol **39** (10 g, 50 mmol) was added in portions over 10 min and the mixture heated at 50°C for 20 min before warm water (100 cm^3) was added and heating continued for a further 20 min. The mixture was evaporated, additional water (100 cm^3) added and the evaporation repeated to give an oil. The latter was dissolved in dichloromethane (100 cm^3) and the solution washed with hydrochloric acid (2 mol dm^{-3}; 50 cm^3) and aqueous sodium hydrogen carbonate (50 cm^3). Evaporation of the organic layer gave a viscous oil which was shown by IR analysis to contain an ester by-product (ν_{max} 1725 cm^{-1}). The oil was dissolved in methanol (75 cm^3) and the solution stirred with aqueous ammonia (d = 0.880; 10 cm^3) for 10 min, evaporated and the residue dissolved in dichloromethane (100 cm^3). The solution was washed with water (50 cm^3), dried, treated with charcoal and filtered through a Celite pad. Evaporation of the filtrates gave the crude *formamido-alcohol* **42** which was triturated with ice-cold diethyl ether, filtered and dried *in vacuo* (8 g, 70%) m.p. 140–141°C. A pure sample (from 2-propanol) had m.p. 143–144°C; Sph. C8, M.P. MeCN:TEAF (30:70), F.R. 2.0 cm^3 min^{-1}, R.T. 4.68 min (1.8%) and 5.17 min (98.2%); Chir. AS, M.P. 2-propanol, F.R. 0.5 cm^3 min^{-1}, R.T. 7.48 min (4.2%), 9.42 min (0.1%), 12.57 min (47.7%) and 25.53 min (48.0%) (Found: C, 73.2; H, 6.6; N, 6.0. $C_{14}H_{15}NO_2$ requires C, 73.4; H, 6.55; N, 6.1%); ν_{max}(Nujol)/cm^{-1} 3440 (OH), 1660 (3° amide), 1640 (conj. C = C) and 1600sh (Ar C = C); δ_H(250 MHz) 1.91 (1H, qd, *J* 5.9 and 12.4, 5-H), 2.05–2.41 (2H, m, 2-OH and 5-H), 2.74–3.25 (3H, m, 3-H and 6-H_2), 3.85 (2/3H, dd, *J* 11.9 and 5.4, 2/3 × 3-H), 4.11 (1/3H), d, *J* 12.5. 1/3 × 4a-H), 4.38–4.60 (2 + 1/3H, m, 2-H and 1/3 × 3-H), 4.70 (2/3H, d, *J* 12.6, 2/3 × 4a-H), 6.14–6.20 (1H, 2 × s, ratio 2:1, 1-H), 7.11–7.25 (3H, m, 7,8,9-H), 7.49 (1H, dd, *J* 7.5 and 1.5, 10-H) and 8.13–8.30 (1H, 2 × s, ratio 2:1, CHO).

2-Chloro-4-formyl-2,3,4,4a,5,6-hexahydrobenzo[f]quinoline (43)

Thionyl chloride (97%; 0.15 cm^3, 2 mmol) was added to a stirred solution of the formamido-alcohol **42** (229 mg, 1 mmol) in dichloromethane (10 cm^3). The mixture was stirred for 0.5 h and evaporated (< 40°C) to give a viscous oil. The latter was dissolved in toluene (10 cm^3) and the solution evaporated under a high-vacuum (< 40°C) to give the *chloride* **43** as a yellow oil (235 mg, 95%); ν_{max}(film)/cm^{-1} 1710–1690 (3° amide; mixture of α- and β-epimers), 1640 (conj. C = C) and 1600w (Ar C = C); δ_H(300 MHz) 1.90–2.07 (1H, m, 5-H), 2.11–2.35 (1H, m, 5-H), 2.97–3.45 (2 + 1/2H, m, 1/2 × 3-H + 6-H_2), 3.75 (1/2H, m, 1/2 × 3-H), 3.98–5.03 (3H, 5 × m, 2-H + 3-H + 4a-H), 6.22–6.29 (2/3H, 2 × br s, 2/3 × 1-H), 6.36–6.42 (1/3H, 2 × br d, *J* 2.0, 1/3 × 1-H), 7.15–7.34 (3H, m, 7,8,9-H), 7.53 (1H, t, *J* 8.3, 10-H), 8.20 (1/3H, br s, 1/3 × CHO), 8.22 (1/3H, br s, 1/3 × CHO), 8.36 (1/6H, br s, 1/6 × CHO) and 8.49 (1/6H, br s, 1/6 × CHO).

4-Formyl-2,3,4,4a,5,6-hexahydrobenzo[f]quinoline-2-carbonitrile (44)

Sodium iodide (99%; 12 g, 80 mmol) was dried *in vacuo* for 1 h at 60°C and dissolved with stirring in acetonitrile (60 cm^3). Simultaneously, pyridine (99%; 3.3 cm^3, 40 mmol) was added to a stirred solution of the formamido-alcohol **42** (8 g, 35 mmol) in dichloromethane (40 cm^3) and the mixture cooled to 3°C before thionyl chloride (97%; 3 cm^3, 40 mmol) was added in one portion. The mixture was stirred for 0.5 h before being washed with hydrochloric acid (1 mol dm^{-3}; 2 × 50 cm^3), dried ($MgSO_4$), treated with charcoal and filtered through a Celite pad. The filtrates were evaporated to give the oily *chloride* **43** (ν_{max}(film)/cm^{-1} 1679 (3° amide), 1638 (conj. C = C) and 1600w (Ar C = C). The latter was dissolved in acetonitrile (100 cm^3) and added to a vigorously stirred suspension of copper (I) cyanide (99%; 25 g, 0.3 mol) in acetonitrile (50 cm^3). The mixture was cooled to 3°C, the sodium iodide solution added in one portion and the mixture stirred overnight at room temperature. Benzene (150 cm^3) (CARE-CARCINOGEN) was added and the mixture stirred for 15 min before being filtered through a Celite pad and the residue washed with fresh benzene (50 cm^3). The filtrates were stirred for 5 min with aqueous sodium thiosulphate solution (0.2 mol dm^{-3}; 200 cm^3), the mixture filtered through a Celite pad and the colourless organic layer evaporated. The residue was treated with boiling dichloromethane (200 cm^3) and the mixture filtered through a Celite pad, dried and evaporated to give an oil. The latter was stirred with diethyl ether–methanol (10:1, 10 cm^3) and the crude *formamido-nitrile* **44** isolated by filtration, washed with ice-cold diethyl ether–methanol (1:1, 5 cm^3) and dried *in vacuo* (3.8 g, 40%), m.p. 180–183°C. A pure sample (from much boiling methanol) had m.p. 186–189°C; Sph. C8, M.P. MeCN:TEAF (30:70), F.R. 2.0 cm^3 min^{-1}, R.T. 4.70 min (0.3%), 11.52 min (99.6%) and 16.38 min (0.1%); Chir. AS, M.P. EtOH, F.R. 0.5 cm^3 min^{-1}, R.T. 5.72 min (0.1%), 15.00 min (49.7%) and 18.48 min (50.2%)

(Found: C, 75.2; H, 5.9; N, 11.6. $C_{15}H_{14}N_2O$ requires C, 75.6; H, 5.9; N, 11.8%); ν_{max}(Nujol)/cm^{-1} 2232 (CN), 1671 (3° amide), 1646 (conj. C = C) and 1600sh (Ar C = C); δ_H(250 MHz) 1.91 (1H, qd, *J* 12.4 and 6.0, 5-H), 2.10–2.35 (1H, m, 5-H), 2.96–3.29 (2H, m, 6-H_2), 3.48–3.58 (2H, m, 2-H and 3-H), 3.85–3.94 (3/4H, m, 3/4 × 3-H), 4.32–4.41 (1/4H, m, 1/4 × 3-H), 4.66 (1/4H, d, *J* 13.0, 1/4 × 4a-H), 4.92 (3/4H, d, *J* 13.0, 3/4 × 4a-H), 6.13–6.21 (1H, 2 × d, *J* 6.0, ratio 3:1, 1-H), 7.13–7.30 (3H, m, 7,8,9-H), 7.47–7.57 (1H, m, 10-H), 8.25 (3/4H, s, 3/4 × CHO) and 8.44 (1/4H, s, 1/4 × CHO).

2,3,4,4a,5,6-Hexahydrobenzo[f]quinoline-2-carbonitrile Hydrochloride (46)

A stirred mixture of the formamido-nitrile **44** (1.0 g, 4 mmol), methanol (20 cm^3) and hydrochloric acid (12 mol dm^{-3}; 2 cm^3) was gently refluxed for 4 h, cooled and left overnight at room temperature. The crude *hydrochloride* **46** was isolated by filtration, washed with diethyl ether and dried *in vacuo* (780 mg, 79%) m.p. 238–239°C. Evaporation of the filtrates gave a yellow solid which on trituration with warm 2-propanol gave a second crop of material (120 mg, 12%) m.p. 225–227°C. A pure sample (from methanol containing 1 drop of 2 mol dm^{-3} hydrochloric acid) had m.p. 238–239°C (Found: C, 67.98; H, 6.80; N, 11.22. $C_{14}H_{14}N_2HCl$ requires C, 68.15; H, 6.13; N, 11.36%); ν_{max}(Nujol)/cm^{-1} 2720, 2600 and 2470 (NH_2^+) and 1595 (Ar C = C); δ_H(300 MHz; D_2O) 1.65–1.83 (1H, m, 5-H), 2.17–2.25 (1H, m, 5-H), 2.82–2.90 (2H, m, 6-H_2), 3.33–3.41 (1H, m, 3-H), 3.84 (1H, dd, *J* 12.5 and 6.3, 3-H), 3.95–4.02 (1H, m, 2-H), 4.12–4.19 (1H, m, 4a-H), 6.32 (1H, br s, 1-H), 7.09–7.31 (3H, m, 7,8,9-H) and 7.57–7.60 (1H, m, 10-H).

2,3,4,4a,5,6-Hexahydrobenzo[f]quinoline-2-carbonitrile (47)

Aqueous sodium hydroxide (2 mol dm^{-3}; 0.25 cm^3, 0.5 mmol) was added in portions to a solution of the hydrochloride **46** (123 mg, 0.5 mmol) in aqueous methanol (1:1; 4 cm^3). The mixture was cooled in ice-water and on scratching a crystalline product began to separate. After additional cooling for 0.5 h, the crude *amino-nitrile* **47** was isolated by filtration, washed with ice-cold water and dried *in vacuo* (100 mg, 95%), m.p. 140–142°C. A pure sample (from 1:1 benzene (CARE-CARCINOGEN)-isopropyl ether) had m.p. 145–146°C (Found: C, 79.97; H, 6.75; N, 13.26. $C_{14}H_{14}N_2$ requires C, 79.96; H, 6.71; N, 13.32%); ν_{max}(Nujol)/cm^{-1} 3320 (NH) 2240 (CN), 1630w (conj. C = C) and 1600w (Ar C = C); δ_H(300 MHz) 1.74–1.92 (2H, m, 5-H_2), 2.19–2.27 (1H, m, N-H), 2.93–3.10 (2H, m, 6-H_2), 3.17 (1H, dd, *J* 13 and 4.3, 3-H), 3.37–3.41 (1H, m, 2-H), 3.51 (1H, d, *J* 13, 3-H), 3.58–3.64 (1H, m 4a-H), 6.24 (1H, d, *J* 5.4, 1-H) 7.17–7.32 (3H, m, 7,8,9-H) and 7.58 (1H, dd, *J* 7.3 and 1.8, 10-H).

4-Methyl-2,3,4,4a,5,6-hexahydrobenzo[f]quinoline-2-carbonitrile Hydrochloride Hemihydrate (49)

Methyl iodide (99%; 172 mg, 1.2 mmol) was added with stirring to a suspension of the amino-nitrile **47** (210 mg, 1 mmol) in ethyl acetate (10 cm^3). Stirring was continued for 0.5 h when anhydrous calcium carbonate (99%; 250 mg, 2.5 mmol) was added and the resulting mixture stirred vigorously overnight. The mixture was filtered and the residue washed with ethyl acetate (2 × 5 cm^3). The combined filtrates were evaporated to give an oil. The latter was dissolved in a mixture of 2-propanol (5 cm^3) and hydrochloric acid (2 mol dm^{-3}; 0.5 cm^3) and the solution evaporated to yield a solid. The process above was repeated twice more to give the crude *amino-nitrile hydrochloride hemihydrate* **49** (160 mg, 59%), m.p. 173–175°C A pure sample (from 5:1 2-propanol/2 mol dm^{-3} hydrochloric acid) had m.p. 177–178°C (Found: C, 66.40; H, 6.69; N, 10.24. $C_{15}H_{16}N_2HCl$. 0.5 H_2O requires C, 66.78; H, 6.72; N, 10.39%); ν_{max}(Nujol)/cm^{-1} 3400 and 3340 (H_2O), 1640 (conj. C = C) and 1600w (Ar C = C); δ_H(300 MHz) 1.68 (1H, qd, *J* 12.5 and 5.9, 5-H), 2.44–2.56 (1H, m, 5-H), 2.72–2.95 (2H, m, 6-H_2), 3.03 (3H, s, N-CH_3), 3.52 (1H, dd, *J* 13.5 and 5.8, 3-H), 3.81–3.92 (2H, m, 2-H and 3-H), 4.05–4.11 (1H, m, 4a-H), 6.34 (1H, d, *J* 4.5, 1-H), 7.06–7.26 (3H, m, 7,8,9-H) and 7.50 (1H, d, *J* 7.9, 10-H)

Summary of the Crystal Data

Methyl 2-Oxo-2,3,4,4a,5,6-hexahydrobenzo[f]quinoline-4-carboxylate (9) (Figure 1)

A crystal was obtained as a prism from acetone/diethylketone/DMF with approximate dimensions 0.38 × 0.12 × 0.12 mm^3 and used for data collection. $C_{15}H_{15}NO_3$ M = 257.28, monoclinic, space group $P2_1/n$, with $a = 1012.9(2)$, $b = 1056.3(3)$, $c = 1190.0(2)$ pm, $\alpha = 90°$, $\beta = 101.915(10)°$, $\gamma = 90°$, $V = 1.2458(4)$ nm^3, $D_x = 1.372$ mg m^{-3}, $Z = 4$, μ(Cu–Kα) = 0.785 mm^{-1}, $F(000) = 544$.

$\lambda = 154.178$ pm, $T = 203(2)$ K, 1689 reflections measured ($5.23 \leq \theta \leq 55.33°$, $0 \leq h \leq 10$, $0 \leq k \leq 11$, $-12 \leq l \leq 12$), 1585 unique reflections used ($R_{int} = 0.0266$).

Full-matrix least squares refinement of 184 parameters for 1582 independent reflections [$I \geq 2\sigma(I)$] gave final R_1- and wR_2-values of 0.0461 and 0.1128 ($R_1 = 0.0626$ and $wR_2 = 0.1285$ for all data).

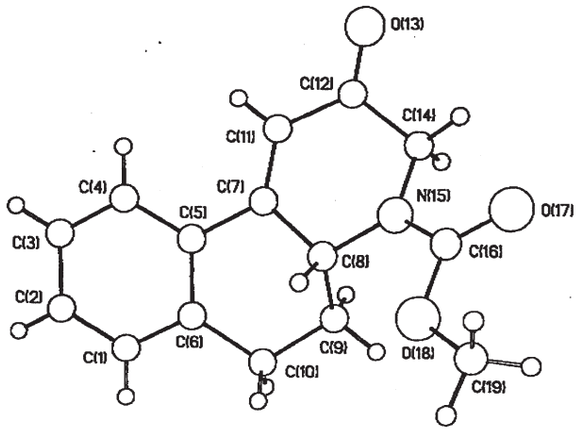


FIGURE 1 Crystal structure of Methyl 2-Oxo-2,3,4,4a,5,6-hexahydrobenzo[*f*]quinoline-4-carboxylate **9**.

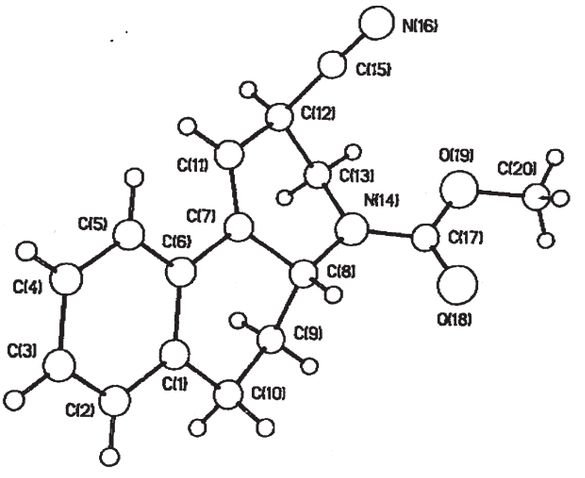


FIGURE 2 Crystal structure of Methyl 2-Cyano-2,3,4,4a,5,6-hexahydrobenzo[*f*]quinoline-4-carboxylate **35**.

Methyl 2-Cyano-2,3,4,4a,5,6-hexahydrobenzo[f]quinoline-4-carboxylate (35) (Figure 2)

A crystal was obtained as a prism from methanol with approximate dimensions $0.25 \times 0.13 \times 0.11\,mm^3$ and used for data collection. $C_{16}H_{16}N_2O_2$, M = 268.31, orthorhombic, space group Pbca, with $a = 1458.44(11)$, $b = 2223.7(2)$, $c = 838.70(6)\,pm$, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, $V = 2.7200(3)\,nm^3$, $D_x = 1.310\,mg\,m^{-3}$, $Z = 8$, $\mu(Cu{-}K\alpha) = 0.707\,mm^{-1}$, $F(000) = 1136$.

$\lambda = 154.178\,pm$, $T = 203(2)\,K$, 1769 reflections measured ($3.98 \le \theta \le 56.07°$, $0 \le h \le 15$, $0 \le k \le 23$, $0 \le l \le 9$), 1769 unique reflections used ($R_{int} = 0.0000$).

Full-matrix least squares refinement of 194 parameters for 1769 independent reflections [$I \ge 2\sigma(I)$] gave final R_1- and wR_2-values of 0.0432 and 0.0979 ($R_1 = 0.0658$ and $wR_2 = 0.1120$ for all data).

2,3,4,4a,5,6-Hexahydrobenzo[f]quinoline-2-carbonitrile Hydrochloride (46) (Figure 3)

A crystal was obtained as a needle from methanol/2 mol dm^{-3} hydrochloric acid with approximate dimensions $0.37 \times 0.10 \times 0.04\,mm^3$ and used for data collection. $C_{14}H_{15}ClN_2$, M = 246.73, orthorhombic, space group Pccn, with $a = 1457.8(2)$, $b = 2171.7(3)$, $c = 838.55(12)\,pm$, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, $V = 2.6549(6)\,nm^3$, $D_x = 1.235\,mg\,m^{-3}$, $Z = 8$, $\mu(Cu{-}K\alpha) = 2.424\,mm^{-1}$, $F(000) = 1048$.

$\lambda = 154.178\,pm$, $T = 203(2)\,K$, 1719 reflections measured ($3.65 \le \theta \le 56.03°$, $-13 \le h \le 15$, $-12 \le k \le 23$, $-2 \le l \le 8$), 1769 unique reflections used ($R_{int} = 0.0000$). Refdelf correction was applied for absorption.

Full-matrix least squares refinement of 172 parameters for 1719 independent reflections [$I \ge 2\sigma(I)$] gave final R_1- and wR_2-values of 0.0477 and 0.1097 ($R_1 = 0.0756$ and $wR_2 = 0.1273$ for all data).

RESULTS AND DISCUSSION

Our immediate objective was an improved synthesis of the precursor *N*-methoxycarbonyl-keto-acid (**5**) starting from 2-oxo-4-phenylbutanoic acid (**10**)[22] *via* the triester (**14**). Condensation of the acid (**10**) with methyl carbamate according to the procedure of Shin *et al.*[23] yielded the unsaturated carbamic ester acid (**11**), which was readily reduced to the saturated ester acid (**12**). The latter was then converted to its dimethyl ester (**13**) by the method of Cohen and Mier.[24] Our next stage, involving *N*-alkylation of the diester (**13**) with methyl chloroacetate alone or in the presence of sodium hydride to yield the crucial

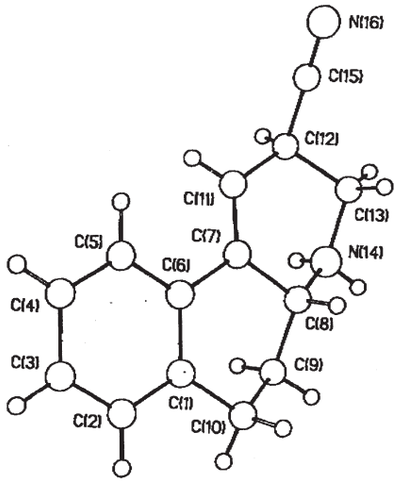
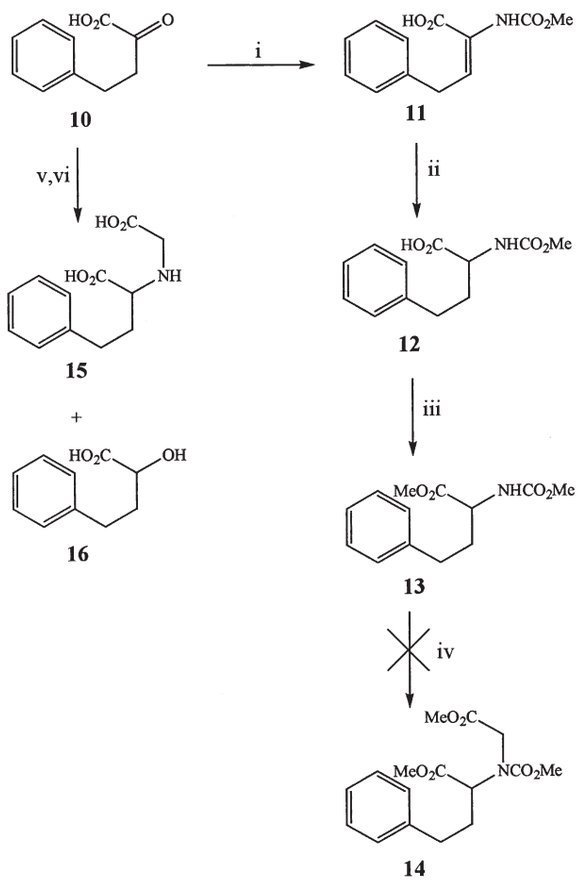


FIGURE 3 Crystal structure of 2,3,4,4a,5,6-Hexahydrobenzo[*f*]-quinoline-2-carbonitrile hydrochloride **46**.



SCHEME 2 Reagents and conditions: i, NH_2CO_2Me, TsOH, PhH, 82°C (41%); ii, 10% Pd/C, H_2, Me_2CHOH (85%); iii, $(MeO)_3CH$, cat. H_2SO_4, MeOH, reflux, 6 h (95%); iv, MeO_2CCH_2Cl, NaH, DMF, rt, 25 min; v, $H_2NCH_2CO_2Na$, H_2O, TsOH, 10% Pd/C, H_2, rt, 1.5 h; vi, 2 mol dm^{-3} HCl (1 equiv.).

intermediate **14**, failed and this method was abandoned (Scheme 2).

A second approach utilising the keto-acid (**10**) involved reductive amination with sodium glycinate in aqueous media in the presence of hydrogen and 10% palladium/charcoal. Uptake of gas was satisfactory but the method gave variable yields (30–60%) of the required amino-diacid (**15**) together with the α-hydroxy-acid (**16**)[25] arising from reduction of the starting keto-acid. In most cases the α-hydroxy acid (**16**) was the major product and again the method was abandoned (Scheme 2).

The ultimately successful approach involved the development of a novel five stage one-pot Strecker-type reaction[26–28] starting from 3-phenylpropionaldehyde (**17**), which was first converted to its sodium bisulphite adduct (**18**) *in situ*. Aqueous sodium glycinate was then added followed later by potassium cyanide to yield, presumably, the sodium and/or potassium salt of cyano-amino-acid (**19**). A large excess of concentrated hydrochloric acid was then added and the mixture refluxed for 7 h and allowed to cool overnight when the crystalline hemihydrochloride (**20**) separated in variable yields (50–60%).

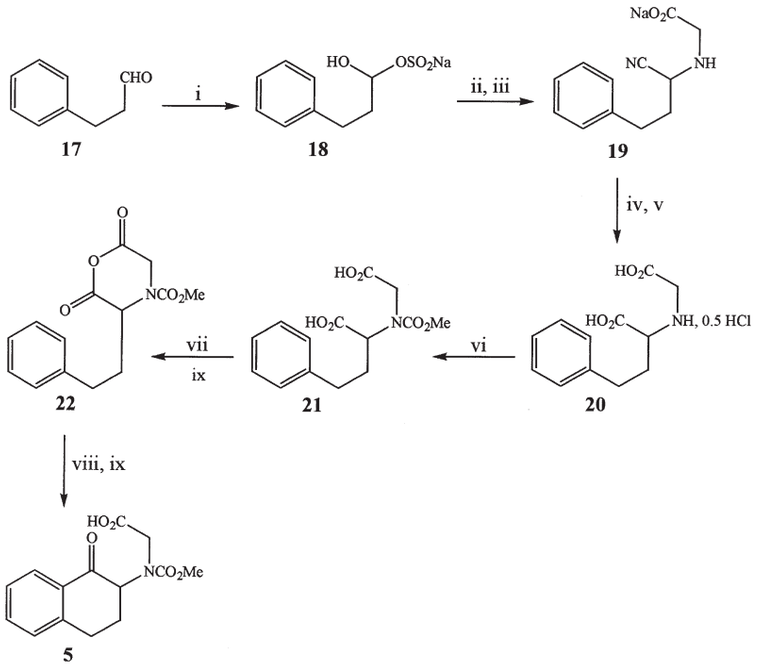
Fortunately, after a prolonged period of optimisation experiments, it was accidentally discovered that overnight stirring of the final reaction mixture consistently gave the crystalline hemihydrochloride (**20**), albeit contaminated with some tar. The latter was readily removed using acetone-diethyl ether washes to give the crucial hemihydrochloride (**20**) repeatedly in the high overall yield of 91%, equivalent to an average of *ca*. 97% in each of the 5 stages involved (Scheme 3).

The hemihydrochloride (**20**) was readily converted into the *N*-methoxycarbonyl-diacid (**21**). Conversion of the latter into the corresponding anhydride (**22**) and reaction of this compound under standard Friedel–Crafts acylating conditions[29] furnished our first target, the *N*-methoxycarbonyl-keto-acid (**5**) in 61% yield (Scheme 3).

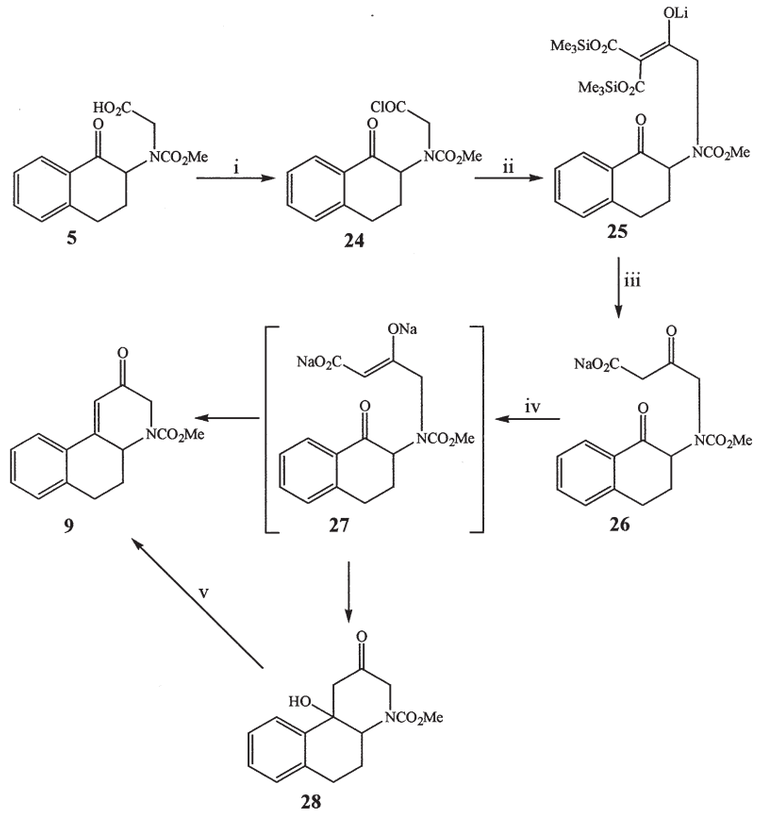
This reaction is especially interesting because of a literature report[30] describing the decarbamoylation of the *N*-methyl-*N*-ethoxycarbonyl amino acid chlorides (**23**) under Friedel–Crafts conditions. This process did not occur when the 2-methyl group was absent and the expected acylation took place (Scheme 3). It appears therefore that the employment of an anhydride as the acylating agent avoids this problem.

With reasonable supplies of the *N*-methoxycarbonyl-keto-acid (**5**) now available, we were able to concentrate our efforts to improve the yields of our second target, the tricyclic ketone (**9**). It was soon found that the keto-acid (**5**) formed a stable acid chloride (**24**) (Scheme 4). We were therefore in a position to employ the elegant β-keto-acid synthesis of Barnick *et al.*[1] involving reaction of the acid chloride (**24**) with lithio-bis(trimethylsilyl)malonate (1:2) at −78°C → 0°C followed by treatment with excess of ice-cold aqueous sodium hydrogen carbonate. The resulting weakly alkaline aqueous solution containing the sodium salt (**26**) was stable at 0°C for at least 3 weeks presumably since the solution was not sufficiently alkaline to generate the sodium enolate (**27**) required for cyclisation. The solution of (**26**) on heating at 60°C–65°C for 0.5 h furnished *via* (**27**) the tricylic ketone (**9**) in 55% yield together with a smaller quantity of the hydroxy-ketone (**28**). From the latter, an additional 13% of (**9**) was obtained by treatment with toluene-*p*-sulphonic acid in boiling benzene, making a total yield of 68% of the crucial tricyclic ketone (**9**) (Scheme 4). The structure of (**9**) was confirmed by X-ray analysis and the crystal structure for (**9**) is given in the Experimental section and shown in Figure 1.

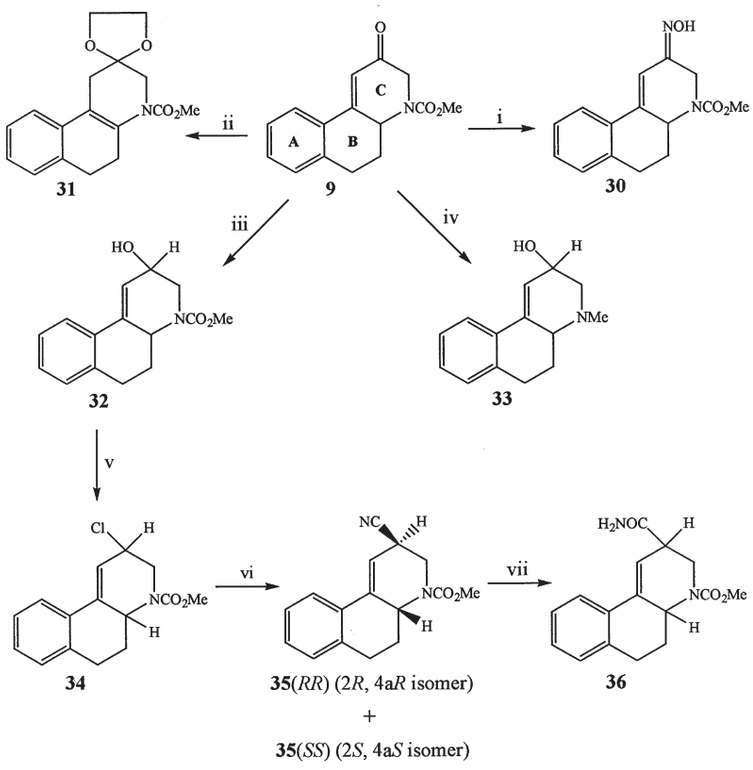
With reasonable quantities of the tricyclic ketone (**9**) at hand, we were now in a position to make progress towards our ultimate target, the *N*-methyl-amino-acid (**29**) and its amides.



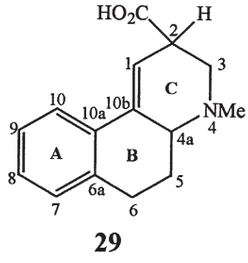
SCHEME 3 Reagents and conditions: i, $Na_2S_2O_5$, H_2O, rt, 1 h; ii, H_2O, $H_2NCH_2CO_2Na$, 34°C, 30 min; iii, KCN, rt, 2.5 h; iv, conc. HCl, 106°C, 7 h; v, stir, 14 h, 10–20°C (91%); vi, $ClCO_2Me$, H_2O, $NaHCO_3$, 3°C, 15 h, HCl (90%); vii, $(CF_3CO)_2O$, CH_2Cl_2, rt, 1 h; viii, $AlCl_3$, CH_2CL_2, −15 to 3°C, 5 h; ix, HCl, H_2O, ice, rt (61%).



SCHEME 4 Reagents and conditions: i, $(COCl)_2$, cat. DMF, PhH, rt, 1 h; ii, $LiCH(CO_2SiMe_3)_2$, −78 to 0°C; iii, $NaHCO_3$, ice-H_2O; iv, 60–65°C, 0.5 h (55%); v, *p*-TsOH, PhH, 82°C, 0.5 h (68% overall yield of **9**).



SCHEME 5 Reagents and conditions: i, NH_2OH, HCl, H_2O, EtOH, K_2CO_3, 50°C, 0.5 h; ii, $(CH_2OH)_2$, $BF_3.Et_2O$, DCM, rt, 24 h (66%); iii, $NaBH_4$, EtOH-H_2O (8:1), 0.5 h rt (94%); iv, DIBAL-H, DCM, 3°C, 3 h (58%); v, $SOCl_2$, DCM, rt, 0.5 h (97%); vi, NaI, CuCN, MeCN, rt, 24 h (70%); vii, 30 wt % H_2O_2 (2 equiv.), Me_2CO_2, 2 mol dm^{-3} NaOH, 60 min (55%).



Two derivatives of the tricyclic ketone (**9**) were prepared by standard procedures to evaluate the activity of the carbonyl group, *viz* the oxime (**30**) (95%) and the ketal (**31**) (66%) in which the double bond had migrated into ring B clearly shown by the absence of an olefinic proton at *ca.* δ 6.50 in its ^{1}H NMR spectrum. In addition, the tricyclic ketone (**9**) was readily reduced using sodium borohydride in aqueous ethanol to give the corresponding tricyclic alcohol (**32**) (94%) whose ^{1}H NMR spectrum clearly indicated that reduction had occurred with exclusive 1,2 addition (an olefinic proton was clearly present at *ca.* δ 6.50) (Scheme 5).

Reduction of the carbonyl group in (**9**) introduced a second chiral centre into the molecule. Thus, there were now four possibilities with regard to the relative configuration of the two chiral centres in the tricyclic alcohol (**32**).

Non-chiral HPLC analysis of (**32**) displayed only a single major peak (99.4%) suggesting that only one of the possible enantiomeric pairs was present *i.e.* either (**32*RR***) + (**32*SS***) or (**32*SR***) + (**32*RS***).

This conclusion was confirmed by chiral HPLC studies which showed that only two enantiomers were present in roughly equal proportion (50.0%:49.7%).

These facts show clearly that a highly stereoselective hydride reduction had been achieved employing a non-chiral reducing agent, presumably due to differences in the ease of approach to the carbonyl group from one or other face of the molecule.

We were particularly keen to obtain at this stage the absolute configuration of the 2-hydroxy group in the tricylic alcohol (**32**) in order to follow the mechanisms involved in subsequent substitution reactions in the 2-position. A number of attempts were made to obtain the configuration using single-crystal X-ray diffraction, without success.

Reduction of the ketone (**9**) with diisobutylaluminium hydride (DIBAL-H)[31] gave the corresponding *N*-methyl alcohol (**33**) as a crystalline solid, mp 144–145°C. Previously, this compound had been reported in the literature as an oil.[32] Again, its ^{1}H NMR

spectrum demonstrated that the carbonyl group had been reduced with exclusive 1,2 addition of hydride ion (Scheme 5).

Our next objective was to convert the alcohol (**32**) into the nitrile (**35**) *via* the corresponding chloride (**34**). However, the latter was recovered unchanged when reacted with sodium cyanide in acetonitrile under anhydrous conditions. This result was probably due to the fact that the cyanide ion present was not a strong enough nucleophile to displace the chloride ion. It was therefore decided to proceed *via* the corresponding iodide. In addition, several authors have reported the superiority of copper (I) cyanide over sodium cyanide of the conversion of alkyl halides into the corresponding cyanides.[33–36] A report has also appeared in the literature detailing stereoselective syn-S_N2 nucleophilic displacements in allylic systems. These displacements are co-ordinated by the addition of the copper species present in the reaction medium to one face of the double bond[37] and it was hoped that such a co-ordination might deliver a facial selectivity during the production of the nitrile. In the event, conversion into the nitrile (**35**) was eventually achieved in moderately high yield (70%) by reaction with copper (I) cyanide in acetonitrile in the presence of sodium iodide (Scheme 5). This reaction appeared to be accompanied by a small amount of competing elimination, the products of which were readily removed by washing the crude product with diethyl ether. Interestingly, when copper (I) cyanide was added *ca.* twelve hours after iodide formation, no nitrile could be isolated on work-up. These observations appear to indicate that the iodide was unstable and would readily undergo elimination reactions in the absence of cyanide ion. The overall yield of the *N*-methoxycarbonyl nitrile (**35**) from the corresponding ketone (**9**) was 66%. The ease with which the nitrile functionality was introduced together with the stability exhibited by the intermediate chloride (**34**) are attributed to the neutralisation of the C-ring nitrogen during the synthesis, which was planned[18] from the very beginning to avoid the severe problems associated with the later stages (OH → Cl → CN) of the Woodward–Kornfeld synthesis[15] where the nitrogen atom was basic, *e.g.* NMe and the reagents were eventually thionyl chloride in liquid sulphur dioxide and sodium cyanide in liquid hydrogen cyanide.

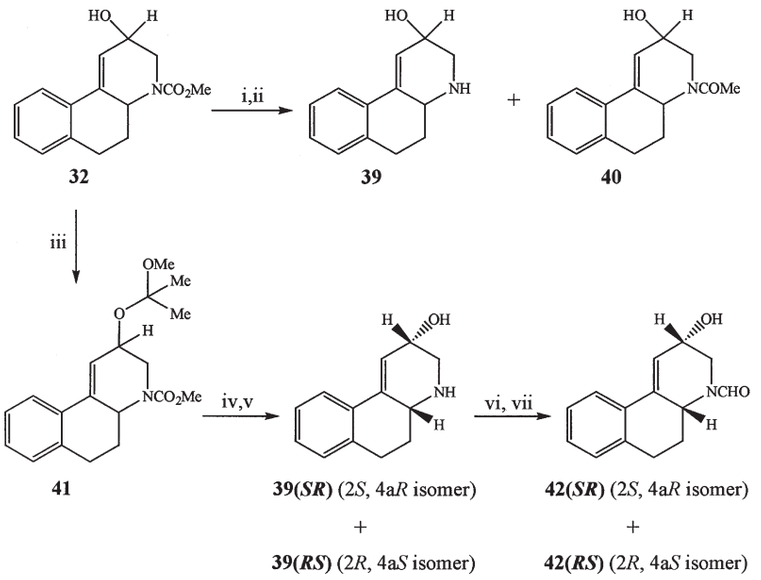
Non-chiral HPLC analysis of the nitrile (**35**) indicated the presence of only one enantiomeric pair in the sample (*i.e.* a single major peak). Chiral HPLC showed two peaks of roughly equal intensity (49.7%:50.3%) confirming the presence of just one enantiomeric pair, *i.e.* either (**35*RR***) and (**35*SS***) or (**35*SR***) and (**35*RS***). Thus, substitution of the OH group had been achieved in a highly stereoselective fashion. The structure of (**35**) was confirmed by X-ray analysis as (***RR***) and (***SS***) and the crystal structure for (**35**) is given in the Experimental section and shown in Figure 2.

Our next objective was hydrolysis of the nitrile (**35**) to give the amide (**36**). The shift in the position of the double bond during the preparation of the ketal (**31**) under strongly acidic conditions at room temperature was a clear warning of the sensitivity of the molecule to such conditions. Accordingly we chose mildly alkaline conditions in the presence of hydrogen peroxide[38] and obtained the amide (**36**) in 55% yield (Scheme 5).

The next stage in the synthetic plan was removal of the now redundant *N*-methoxycarbonyl group in (**36**) using reagents unlikely to damage the stereochemical integrity of the remainder of the molecule. Reagents such as hydrazine hydrate in alkali were ruled out due to their ability to isomerise the C_2-H. The use of sodium hydrogen telluride was also avoided on the grounds of toxicity. The use of trimethylsilyl iodide to remove this protecting group had also been reported by several authors.[39,40] However, when these procedures were applied to the model compound, *N*-carboxymethylisonipecotamide (**38**) (to save **36**), prepared from commercially available isonipecotamide (**37**), only starting material was recovered. The *N*-methoxycarbonyl protecting group had proved to be remarkably resistant to the standard reagents used for its removal, probably due to steric hindrance around the nitrogen atom in the tricyclic intermediates. Therefore, it was decided to replace this group with a more labile function at an earlier stage than originally planned, *via* the amino-alcohol (**39**). Reaction of the tricyclic alcohol (**32**) with methyllithium–lithium bromide in refluxing diethyl ether[41] gave the required amino-alcohol (**39**) (37%) together with a significant quantity (21%) of the corresponding *N*-acetamido derivative (**40**) (ν_{max} 1606 cm^{-1}) (Scheme 6).

The low yield of the amino-alcohol (**39**) and the formation of the amide (**40**) were considered to be due to partial reaction of the methyllithium with the free hydroxyl group in the starting alcohol (**32**). This problem was eventually overcome by conversion of the starting alcohol (**32**) to its methoxypropyl ether (**41**)[42] followed by reaction with the methyllithium reagent, as before. Good yields (*ca.* 75%) of the required tricyclic amino-alcohol (**39**) were subsequently obtained with no *N*-acetamido-alcohol being present (Scheme 6).

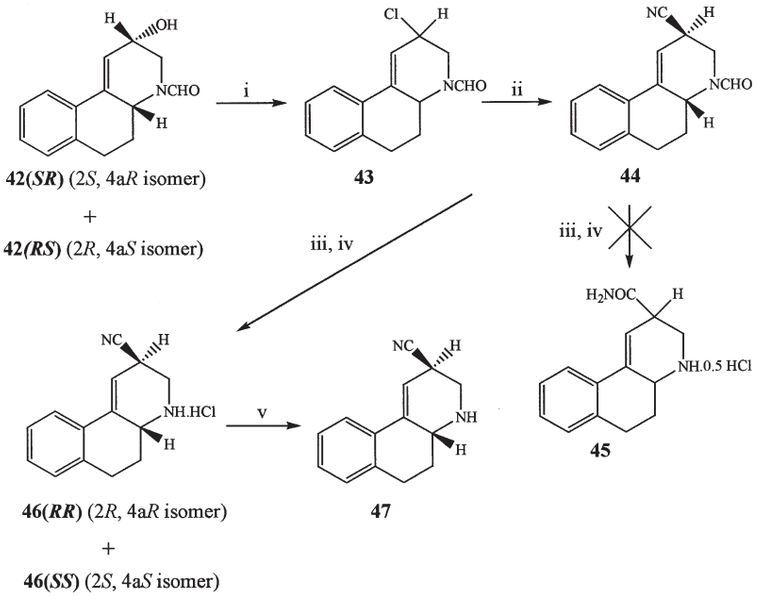
The use of the nucleophilic reagent methyllithium to remove the *N*-methoxycarbonyl group in (**32**) could have led to scrambling of the chiral centre at the 2-position. However, non-chiral HPLC analysis of the amino-alcohol (**39**) revealed that only one pair of enantiomers was present



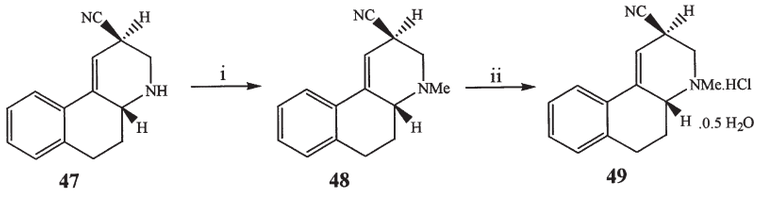
SCHEME 6 Reagents and conditions: i, MeLi-LiBr, Δ; ii, H_2O, iii, p-TsOH, MeC(OMe) = CH_2, Et_2O, 3°C, 0.5 h; iv, MeLi-LiBr, 33°C, 1.5 h; v, H_2O, HCl, NH_4OH, CH_2Cl_2, Et_2O, 0°C (75%); vi, Ac_2O, HCO_2H, 50°C, 20 min; vii, H_2O, 20 min.

(*i.e.* only a single major peak was observed). Chiral HPLC analysis showed two peaks of roughly equal intensity (51.0%:48.7%) confirming the presence of just one enantiomeric pair, which is most probably (**39*SR***) and (**39*RS***). Thus, the removal of the protecting group had been achieved without scrambling of the chiral centre at the 2-position. The amino-alcohol (**39**) now required a stable but readily removed protecting group *viz* the formyl group, which had been found earlier in the project to be readily prepared in good yield (70%) using acetic-formic anhydride[43] formed *in situ* and readily removed under both basic and acidic conditions (Scheme 6).

Non-chiral HPLC analysis of the formamido-alcohol (**42**) revealed that only one pair of enantiomers was present (*i.e.* only a single major peak was observed). Chiral analysis showed two peaks of roughly equal intensity (47.7%:48.0%) confirming the presence of one enantiomeric pair, which is probably (**42*SR***) and (**42*RS***). Thus, protection of the ring nitrogen had not caused epimerisation at the 2-position.



SCHEME 7 Reagents and conditions: i, $SOCl_2$, DCM, rt, 0.5 h; ii, NaI, CuCN, MeCN, rt, 24 h (40%); iii, conc. HCl, MeOH, 40°C, 4 h; iv, rt, 14 h (91%); v, NaOH, H_2O, MeOH, 0°–3°C, 0.5 h (95%).



47 48 49

SCHEME 8 Reagents and conditions: i, MeI, EtAc, $CaCO_3$, rt, 24 h; ii, HCl, Pr^iOH (59%).

Reaction of the formamido-alcohol (**42**) with thionyl chloride gave the corresponding chloride (**43**) as an oil. The latter was then transformed into the *N*-formamido-nitrile (**44**) employing the methodology described for the preparation of the corresponding *N*-methoxycarbonyl nitrile (**35**) (Scheme 7).

Non-chiral HPLC studies on (**44**) showed only one of the possible enantiomeric pairs was present in the sample (*i.e.* only a single peak was observed). Chiral HPLC analysis showed two peaks of roughly equal intensity (49.7%:50.2%) confirming the presence of one enantiomeric pair. Thus, once again substitution of the OH group had been achieved in a highly stereoselective fashion.

The penultimate stage in this project was the removal of the *N*-formyl protecting group from the *N*-formamido-nitrile (**44**), employing concentrated hydrochloric acid in methanol under reflux for 4 h, followed by standing overnight at room temperature from which a crystalline solid was isolated. The infrared spectrum of this product did not show a nitrile peak (*ca.* 2240 cm^{-1}) and it was assumed that the amino-amide hemihydrochloride (**45**) had been obtained. Elemental analysis appeared to confirm this assumption despite the fact that the ^{1}H-NMR spectrum of this compound did not show peaks corresponding to the primary amide protons. Fortunately, the crystal structure of this compound was eventually obtained by X-ray, which showed that the product of this hydrolysis reaction was the required amino-nitrile hydrochloride (**46**) composed of a racemic mixture of (**46*RR***) and (**46*SS***) enantiomers, obtained in 91% yield (Scheme 7). The crystal structure for (**46**) is given in the Experimental section and shown in Figure 3.

Neutralisation of the amino-nitrile hydrochloride (**46**) with care using aqueous sodium hydroxide at 0–3°C furnished the free base (**47**) (ν_{max} 2240 (CN) *etc.*) in 95% yield. It was assumed that under those conditions the stereochemical integrity at the 2-position would be retained. Reaction of the base (**47**) with methyl iodide in ethyl acetate in the presence of anhydrous calcium carbonate (less alkaline than potassium carbonate and therefore less likely to affect the stereochemical integrity at the 2-position) yielded the *N*-methyl base (**48**) as an oil (ν_{max} 2242(CN)). The latter was converted into its hydrochloride hemihydrate salt (**49**) (59%) whose infrared spectrum failed to show a nitrile peak similar to that of the corresponding des-methyl nitrile hydrochloride salt (**46**) (Scheme 8).

The work described above has resulted in a highly stereoselective synthesis of the title compound, albeit in very low yield. Future work on this programme will be targeted at scaling-up the synthesis of (**49**) in order to provide sufficient quantities of the corresponding acid (**29**) for conversion into derivatives of biological interest.

References

[1] Barnick, J.W.F.K., van der Baan, J.L. and Bickelhaupt, F. (1979) *Synthesis* 787.
[2] Ninomiya, I. and Kiguchi, T. (1990) *The Alkaloids* (Academic Press Inc., New York) **Vol. 38**, pp 1–156.
[3] Brazeau, P. (1970) In: Goodman, L.S. and Gilman, A., eds, *The Pharmacological Basis of Therapeutics*, 4th Ed. (Macmillan, New York), pp 897–905.
[4] Nickerson, M. (1970) In: Goodman, L.S. and Gilman, A., eds, *The Pharmacological Basis of Therapeutics*, 4th Ed. (Macmillan, New York), pp 557–559.
[5] Glenn, A.L. (1954) *Quart. Rev.* **8**, 192.
[6] Stoll, A. and Hofmann, A. (1965) In: Manske, R.H.F., ed, *The Alkaloids* (Academic Press Inc., New York) **Vol. 8**, p 725.
[7] Hofmann, A. (1970) In: Ayd, F.J. and Blackwell, B., eds, *Discoveries in Biological Psychiatry* (J.B. Lippincott, Toronto), pp 91–106.
[8] von Békésy, N. (1935) *Hungarian Patent*, 112711.
[9] von Békésy, N. (1938) *Zentr. Bakt. Parasitenk. Abt. II* **99**, 321.
[10] Hecht, W. (1944) *Pharm. Acta Helv.* **19**, 112.
[11] Stoll, A. and Brack, A. (1944) *Pharm. Acta Helv.* **19**, 118.
[12] Flückiger, E. (1972) In: Boyns, A.R. and Griffiths, K., eds, *Prolactin and Carcinogenesis* (Alpha Omega Alpha, Cardiff), pp 162–180.
[13] Flückiger, E. (1975) *Triangle* **14**, 153.
[14] Flückiger, E., Doepfner, W., Markó, M. and Niederer, W. (1976) *Postgrad. Med. J.* **52**, 57.
[15] Bowman, R.E., Evans, D.D., Guyett, J., Weale, J. and White, A.C. (1973) *J. Chem. Soc. Perkin Trans. I*, 760.
[16] Kornfield, E.C., Fornefeld, E.J., Kline, G.B., Mann, M.J., Morrison, D.E., Jones, R.G. and Woodward, R.B. (1956) *J. Am. Chem. Soc.* **78**, 3087.
[17] Bowman, M.A.E. and Bowman, R.E. (1999) *J. Chem. Res. (S)* 94, Part 7.
[18] Bowman, R.E. (1980) *J. Chem. Soc. Perkin Trans. I*, 2126.
[19] Bowman, R.E. (1983) *J. Chem. Soc. Perkin Trans. I*, 897.
[20] Sheldrick, G.M. (1990) *Acta Crystallogr. Sect. A* **46**, 467.
[21] Sheldrick, G.M., *SHELXL-93, Program for the Refinement of Crystal Structures* (University of Göttingen, Germany).
[22] Wislicenus, W. (1898) *Chem. Ber.* **31**, 3133.
[23] Shin, C., Yonezawa, Y., Unoki, K. and Yoshimura, J. (1979) *Tetrahedron Lett.* 1049.

[24] Cohen, H. and Mier, J.D. (1965) *Chem. Ind*. 349.
[25] Dakin, H.D. and Dudley, H.W. (1914) *J. Chem. Soc.* **105**, 2462.
[26] Stout, D.M., Black, L.A. and Matier, W.L. (1983) *J. Org. Chem.* **48**, 5369.
[27] Inaba, T., Fujita, M. and Ogura, K. (1991) *J. Org. Chem.* **56**, 1274.
[28] Inaba, T., Kozono, I., Fujita, M. and Ogura, K. (1992) *Bull. Chem. Soc. Jpn* **65**, 2359.
[29] Olah, G.A. (1964) *Friedel-Crafts and Related Reactions* (Interscience, New York) **Vol. 3**, pp 291–296.
[30] Buckley, T.F. and Rapoport, H. (1981) *J. Am. Chem. Soc.* **103**, 6157.
[31] Yoon, N.H. and Gyoung, Y.S. (1985) *J. Org. Chem.* **50**, 2443.
[32] Leeman, H.G. and Fabbri, S. (1959) *Helv. Chim. Acta* **42**, 2696.
[33] Breckpot, R. (1930) *Bull. Soc. Chim. Belg.* **39**, 466.
[34] Ruylants, P.B. (1922) *Bull. Soc. Chim. Belg.* **31**, 75.
[35] Supniewski, J.V. and Salzberg, P.L. (1941) *Organic Synthesis* **Vol I**, 46, Coll.
[36] Smith, C.W. and Snyder, H.R. (1955) *Organic Synthesis* **Vol III**, 852, Coll.
[37] Yamamoto, Y. and Asao, N. (1990) *J. Org. Chem.* **55**, 5303.
[38] Balicki, R. and Kaczmarek, L. (1993) *Synth. Commun.* **23**, 3149.
[39] Jung, M.E. and Lyster, M.A. (1978) *J. Chem. Soc. Chem. Commun.* 315.
[40] Olah, G.A., Narang, S.C., Gupta, B.G.B. and Malhotra, R. (1979) *J. Org. Chem.* **44**, 1247.
[41] Sawyer, J.S. and Narayanan, B.A. (1983) *Synth. Commun.* **13**, 135.
[42] Reese, C.B., Saffhill, R. and Sulston, J.E. (1967) *J. Am. Chem. Soc.* **89**, 3366.
[43] Mehlenbacher, V.C. (1953) *Org. Analysis* **1**, 37.