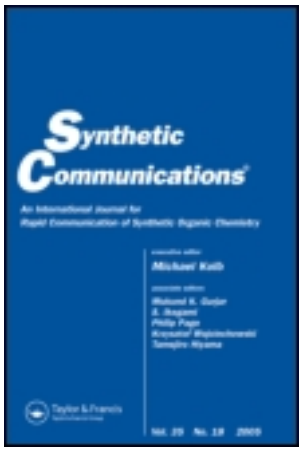

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A Unified Synthesis of Bifunctional 4-Substituted-1,2,3,4-tetrahydroisoquinoline Derivatives

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A Unified Synthesis of Bifunctional 4-Substituted-1,2,3,4-tetrahydroisoquinoline Derivatives

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ABSTRACT

Starting from a single, commercially available bromoisoquinoline, convenient (multigram) syntheses of 4-substituted-1,2,3,4-tetrahydroisoquinoline derivatives have been developed. The compounds thus prepared show suitable substitution patterns for further derivatization and constitute a new family of compounds of potential pharmacological interest.

Key Words: Nucleophilic aromatic substitutions; Protecting groups; Combinatorial chemistry; Copper; Hydrogenation.

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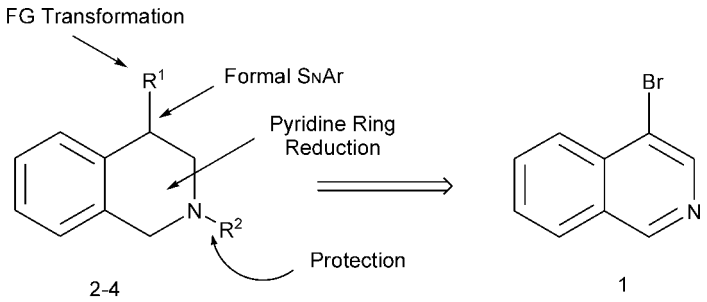
INTRODUCTION

One promising source of new and biologically relevant compounds resides in the development of original (or unexplored) substitution patterns among the so-called *privileged structures.*[1–4] In this context, although tetrahydroisoquinolines can be regarded as the key subunits in many bioactive compounds,[5–9] this *scaffold* still offers opportunities for further development.

Tetrahydroisoquinolines bearing suitable substituents at position 4 (thus displaying two functional points for diversification) could provide *new chemical entities* (NCEs) which may evolve into selective drugs. In the course of a research project, we became interested in these heterocyclic systems, and needed a practical access to such structures.

Some of these compounds have previously been prepared by different methods. However, many of these syntheses involve long sequences, use a broad range of starting materials and routes (and therefore are not connected), and/or are scarcely described in the literature. The present paper deals with the development of a divergent synthesis for a family of these compounds (tetrahydroisoquinoline derivatives **2**–**4**) from a single commercially available isoquinoline in a short and flexible (amenable for diversification) protocol. The retrosynthetic analysis (Sch. 1) basically involves the introduction of the substituent at position 4 through a formal SNAr, the reduction of the pyridine ring moiety and the subsequent functional group transformations (including optional protection steps).



Scheme 1. Retrosynthetic analysis of compounds **2**–**4**.

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RESULTS AND DISCUSSION

Initially we decided to explore the synthesis of 4-hydroxy-1,2,3,4-tetrahydroisoquino-line (**2a**) from 4-bromoisoquinoline **1** as depicted in Sch. 2. It should be noted that the preparation of this compound has been previously described in the literature from phthalaldehyde and from 2-carboxybenzaldehyde through a 3–4 step synthetic sequences.[10–13]

The bromomoisoquinoline **1** was treated with sodium hydroxide in the presence of copper at high temperature, affording the hydroxyisoquinoline **5**, as described in the literature.[14–16]

Alternatively, this compound could also be prepared by diazotization of aminoisoquinoline **7** (see below) in 89% yield.[17] Esterification of **5** was carried out according to a known procedure to yield acetate **6**.[18] The catalytic hydrogenation of acetate **6** (PtO_2, AcOH) afforded a mixture of the expected 4-acetoxy-tetrahydroisoquinoline together with the corresponding 4-hydroxy-*N*-acetamide derivative (probably the result of a spontaneous *O* to *N* acyl transfer). The crude mixture was subsequently subjected to basic hydrolysis to give the desired tetrahydroisoquinoline **2a** in 69% yield. This aminoalcohol was selectively *N*-Boc protected, using standard conditions, to afford hydroxyurethane **2b** in almost quantitative yield. The conversion of the protected alcohol **2b** into the amino derivative **3d** through displacement reactions or an oxidation-reductive amination sequence was tried without success.

The 4-amino(amido) derivatives **3** were obtained from 4-bromoisoquinoline **1** following an analogous procedure: the amination of **1** (autoclave, aqueous ammonia, $CuSO_4$) was performed using a modification of the reported procedure[19] provided the aminoisoquinoline **7** in an improved 98% yield. Treatment of **7** with equimolecular amounts of the corresponding anhydride furnished amides **8a–c**, in excellent yields (method A).

More conveniently, compounds **8a** (41%) and **8b** (83%) have been synthesized directly from 4-bromoisoquinoline **1** by *N*-arylation with acetamide or benzamide respectively (method B), using a modified version of the recently described Buchwald procedure (Sch. 3).[20]

Finally, 4-acylamino-1,2,3,4-tetrahydroisoquinolines **3a–c** were prepared by catalytic hydrogenation of the corresponding amides.[21] However, in this reaction, the isomeric 5,6,7,8-tetrahydro derivatives [for instance, **11a** (16%), **11b** (2%)], resulting from the reduction of the benzene ring, were also produced (Fig. 1). Interestingly, as in the previous series, no hydrogenolytic interference was detected. It should be noted that the attachment of an electron-withdrawing group upon the substituent at position 4 seems to be a requisite for the selective (although not exclusive) reduction of the pyridine ring moiety on 4-hydroxy- and 4-aminoisoquinolines.[22] The basic hydrolysis

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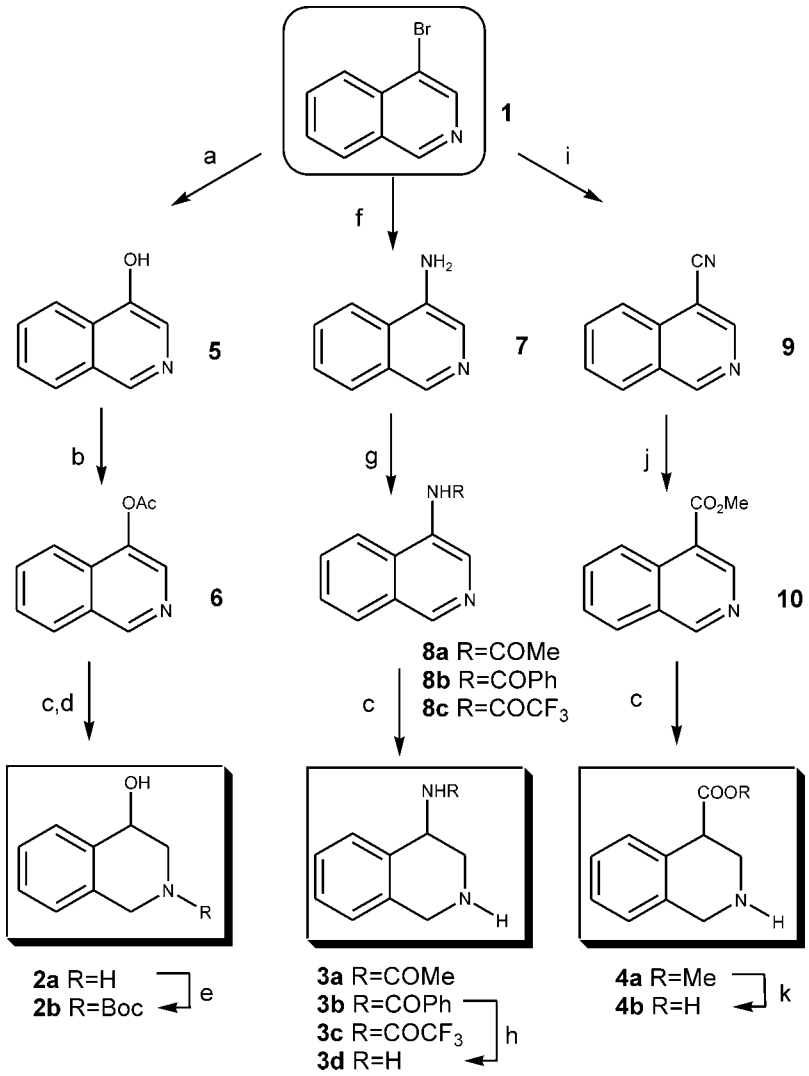

Scheme 2. Reagents and conditions: (a) NaOH, $CuSO_4$, Cu (bronze) 210°C (60%); (b) Ac_2O reflux (71%); (c) H_2 (1 atm), PtO_2, AcOH, rt (71–88%); (d) 3M KOH, reflux (69%); (e) $(Boc)_2O$, Et_3N, CH_2Cl_2 (99%); (f) NH_3(aq), $CuSO_4$, 170°C (98%); (g) $(RCO)_2O$, pyr,100°C (92–99%); (h) 3M KOH, reflux (99%); (i) CuCN, 225°C (81%); (j) MeOH, H_2SO_4, reflux (70%); (k) H_2O reflux (90%).

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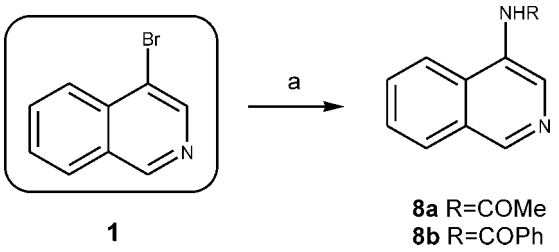

Scheme 3. Reagents and conditions: a) CuI, K_3PO_4, polyethylenimine, acetamide or benzamide. **8a**, dioxane, reflux (41%); **8b**, toluene, reflux (83%).

of benzamide **3b** gave the desired 4-amino-1,2,3,4-tetrahydroisoquinoline **3d** in quantitative yield.

The 1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (**4b**) and its methyl ester **4a** were prepared according to a similar procedure. 4-Bromoisoquinoline was cleanly transformed into nitrile **9** (CuCN, 225°C) in excellent yield.[23] The alcoholysis of **9** using standard conditions ($MeOH-H_2SO_4$) proceeded in 70% yield to afford the corresponding methyl ester **10** and the catalytic hydrogenation of this compound using PtO_2 in AcOH yielded the tetrahydro derivative **4a**. The hydrolysis of the ester function with neat water (probably through an internal general base catalysis) gave the pure β-amino acid **4b** in 90% yield.

EXPERIMENTAL

Melting points were determined in a capillary tube and are uncorrected. TLC was done on Merck silica gel coated plates ($60\,F_{254}$). Flash chromatography was carried out on Merck silica gel (60 A CC, 35–70 μm).

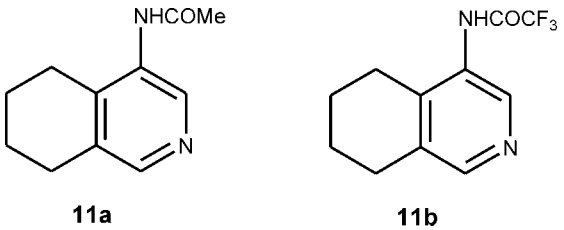

Figure 1. Compounds **11a** and **11b**.

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IR spectra were recorded on a Nicolet 205 FT-IR spectrophotometer. NMR spectra were measured with Varian Gemini-200 (200 MHz) and Varian Gemini-300 (300 MHz) spectrometers. Mass spectra were recorded in the electron impact (EI) mode on a Hewlett-Packard model 5898A. Elemental analyses were performed on a Carlo Erba Instrument EA-1108 in the Serveis Científico-Tècnics de la Universitat de Barcelona.

4-Hydroxyisoquinoline (**5**). A mixture of 4-bromoisoquinoline (10.5 g, 50.5 mmol), hydrated $CuSO_4$ (5 g), copper bronze (4.1 g) and NaOH (31.3 g, 757.5 mmol) in water (17 mL) was heated in an autoclave at 210°C for 12 h. After cooling to room temperature, the dark brown residue was extracted with hot water, and carbon dioxide gas was bubbled through the aqueous extract to precipitate the 4-hydroxyisoquinoline **5** (4.4 g, 60%); mp 223–225°C (EtOH) (lit.[14] 223°C). ^{1}H-NMR (200 MHz, DMSO-d_6): $\delta = 7.64$ (1H, m), 7.70 (1H, m), 8.02 (1H, d, *J* 8.4), 8.04 (1H, s), 8.10 (1H, d, *J* 8.0), 8.78 (1H, s) and 10.35 (1H, br s).

4-Acetoxyisoquinoline (**6**). A mixture of hydroxy derivative **5** (900 mg, 6.16 mmol) and 10 mL of acetic anhydride was stirred at reflux temperature for 5 h. After cooling to room temperature, the solution was concentrated under reduced pressure and the residue was taken up in EtOAc (50 mL), made alkaline (pH = 8) with saturated aqueous $NaHCO_3$ solution, the organic layer was separated and the aqueous phase was extracted with AcOEt (3 × 35 mL). The combined organic layers were dried (Na_2CO_3–Na_2SO_4), filtered and concentrated to afford crude **6** (818 mg, 71%) as a light-yellow oil, which solidified on standing, mp 52–54°C (hexanes), (lit.[24] 54–55°C). ^{1}H-NMR (200 MHz, $CDCl_3$): $\delta = 2.49$ (3H, s), 7.66 (1H, m), 7.75 (1H, m), 7.85 (1H, d, *J* 8.4), 8.03 (1H, d, *J* 8.0), 8.40 (1H, s) and 9.17 (1H, s).

1,2,3,4-Tetrahydro-4-hydroxyisoquinoline (**2a**). PtO_2 (25 mg) was added to a solution of 4-acetoxyisoquinoline (**6**, 250 mg, 1.34 mmol) in AcOH (25 mL), the resulting suspension was hydrogenated (1 atm) at room temperature. After completion of the reaction (TLC control) the catalyst was removed by filtration throught a short pad of celite and the filtrates were concentrated under reduced pressue to afford an oily residue (182 mg, 71%). The residue was taken up in an aqueous solution of KOH (3M, 30 mL) and refluxed for 24 h. The mixture was then diluted with brine and throughly extracted with EtOAc (6 × 20 mL). After drying (K_2CO_3) the solvent was evaporated to give essentially pure aminoalcohol **2a** (138 mg, 69%) as a red viscous oil. IR (film): 3292, 2922, 1449, 1030 and 744 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$): $\delta = 2.94$ (1H, dd, *J* 13.1 and 3.0 Hz), 3.12 (1H, dd, *J* 13.1 and 3.0 Hz), 3.29 (2H, br s), 3.78 (2H, d, *J* 4.8 Hz), 4.48 (1H, t, *J* 3.0 Hz), 6.96 (1H, m), 7.20 (2H, m), 7.34 (1H, m).

***N-tert*-butyloxycarbonyl-4-hydroxy-1,2,3,4-tetrahydroisoquinoline** (**2b**). A solution of 1,2,3,4-tetrahydro-4-hydroxyisoquinoline **2a** (89 mg,

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0.60 mmol) in dry CH_2Cl_2 (6 mL) was stirred at 0°C under nitrogen atmosphere. Di-*tert*-butyl-dicarbonate (143 mg, 0.65 mmol) and Et_3N (90 μL, 0.65 mmol) were then added to the solution, and the resulting mixture was stirred for 4 h at room temperature. The solvent was removed under reduced pressure and the residue was taken up in EtOAc (10 mL) and washed with saturated aqueous $NaHCO_3$ solution and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated to yield **2b** (148 mg, 99%) as yellow oil. IR (film): 3420, 1682, 1417, 1164, 887 and 748 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$): $\delta = 1.47$ (9H, s), 3.61 (1H, dd, *J* 13.3 and 3.8 Hz), 3.81 (1H, dd, *J* 13.3 and 5.4 Hz), 4.44 (1H, d, *J* 17.0 Hz), 4.71 (2H, m), 7.11 (1H, m), 7.25 (2H, m) and 7.46 (1H, m). ^{13}C-NMR (50.3 MHz, $CDCl_3$): $\delta = 28.5$, 45.6, 48.0, 66.0, 80.3, 125.8, 126.8, 127.7, 128.0, 133.1, 136.7 and 155.2. MS (EI): $m/z = 249$ (M^+, 28) 192 (43), 148 (27), 146 (20), 130 (41), 119 (12), 118 (15), 91 (12) and 57 (100). HRMS: m/z calcd for $C_{14}H_{19}NO_3$: 249.1365; found: 249.1378.

4-Aminoisoquinoline (**7**). A mixture of 4-bromoisoquinoline (10.44 g, 49.2 mmol), concentrated NH_4OH solution (30%, 120 mL) and hydrated $CuSO_4$ (5 g) were heated for 24 h at 165–170°C in an autoclave. The reaction mixture was cooled to room temperature, diluted with an aqueous NaOH (20%, 200 mL) solution and extracted with EtOAc (5 × 200 mL). The organic layer were dried (Na_2SO_4), filtered, treated with decolorizing charcoal, filtered and concentrated under reduced pressure to afford pure aminoisoquinoline **7** (7.0 g, 98%); mp 108–110°C (Et_2O) (lit.[19] 108.5°C). ^{1}H-NMR (200 MHz, $CDCl_3$): $\delta = 4.10$ (2H, m), 7.59–7.75 (2H, m), 7.79 (1H, m), 7.91 (1H, m), 8.05 (1H, s) and 8.75 (1H, s). ^{13}C-NMR (50.3 MHz, $CDCl_3$): $\delta = 120.1$, 126.0, 127.1, 127.8, 128.0, 128.6, 129.0, 137.0 and 143.0 MS (EI): $m/z = 145$ ($M^+ + 1$, 11%), 144 (100), 117 (44), 116 (14), 90 (28), 89 (24).

4-Acetamidoisoquinoline (**8a**). *Method A*: A solution of acetic anhydride (5.2 mmol) in pyridine (1 mL) was added dropwise to a stirred solution of compound **7** (5.2 mmol) in pyridine (5 mL). The reaction mixture was stirred at 100°C under nitrogen atmosphere, and after completion of the reaction (monitored by TLC, reaction time 45 min), it was quenched with saturated aqueous $NaHCO_3$ solution and the resulting mixture was throughly extracted with $CHCl_3$ (5 × 20 mL). The organic extracts were dried (Na_2CO_3 –Na_2SO_4), filtered, and concentrated under reduced pressure to yield essentially pure amide **8a** (93%). An analytically pure sample was obtained through chromatography on silica gel (EtOAc/MeOH/Et_3N 90 : 10 : 2); mp 168–169°C (Hexane/EtOAc) (lit[19] 167–168°C). ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 2.33$ (3H s), 7.58–7.76 (2H, m), 7.84 (1H, d, *J* 8.4 Hz), 8.00 (1H, d, *J* 8.0 Hz), 8.35 (1H, br s), 8.68 (1H, s) and 9.01 (1H, s). *Method B*: To a resealable Schlenk tube, or alternatively a screw-cap test tube, were added CuI (10 mol%), acetamide (1.2 mmol) and K_3PO_4 (2.1 mmol), and the reaction

vessel was fitted with a rubber septum. The vessel was evacuated and back-filled with argon. 4-Bromoisoquinoline (1.0 mmol), polyethylenimine (20 mg), and dioxane (1 mL) were then successively added under a stream of argon. The reaction tube was quickly sealed and the contents were stirred while heating in an oil bath at 100°C until the reaction was finished (10 days). The reaction mixture was cooled to ambient temperature, diluted with EtOAc (2–3 mL), and filtered through a plug of silica gel, eluting with additional EtOAc (10–20 mL). The filtrate was concentrated and the resulting residue was purified by column chromatography to provide the desired product **8a** (41%).

4-Benzamidoisoquinoline (**8b**). Following the method A from 4-bromoisoquinoline and benzoic anhydride (reaction time 1 h 30 min), amide **8b** (92%) was obtained; mp 189–190°C (Hexane/EtOAc) (lit.[19] 188–189°C). ^{1}H-NMR (200 MHz, $CDCl_3$): $\delta = 7.47–7.77$ (5H, m), 7.88 (1H, d, J 7.6 Hz), 7.99 (3H, m), 8.40 (1H, s), 8.87 (1H, s) and 9.12 (1H, s). ^{13}C-NMR (50.3 MHz, $CDCl_3$): $\delta = 120.8$, 127.3, 127.4, 128.0, 128.1, 128.8, 130.7, 130.9, 132.2, 134.0, 139.1, 149.7, 150.6 and 166.5. Following the method B, from 4-bromoisoquinoline and benzamide in toluene at 110°C (reaction time 6 days), amide **8b** (83%) was obtained.

4-Trifluoroacetamidoisoquinoline (**8c**). Following the method A with trifluoroacetic anhydride (reaction time 20 min), amide **8c** (99%) was obtained as a viscous oil. ^{1}H-NMR (200 MHz, $CDCl_3$): $\delta = 7.70–7.84$ (3H, m), 8.07 (1H, d, J 8.0 Hz), 8.65 (1H, br s), 8.82 (1H, s) and 9.22 (1H, s). MS (EI): $m/z = 241$ ($M^+ + 1$, 13%), 240 (M^+, 100%), 145 (17), 128 (27), 117 (14) and 116 (95). HRMS: m/z calcd for $C_{11}H_7F_3N_2O$: 240.0519; found: 240.0510.

General procedure for the preparation of 4-amido-1,2,3,4-tetrahydroisoquinoline derivatives (**3a–c**). A suspension of 4-acylaminoisoquinoline **8** (1.0 mmol) in AcOH (20 mL) and PtO_2 (20 mg) was hydrogenated (1 atm) at room temperature. After completion of the reaction (monitored by TLC), the catalyst was removed by filtration through a short pad of celite and the filtrates were concentrated under reduced pressure. The residue was taken up in $CHCl_3$, basified (pH = 8–9) with an aqueous saturated $NaHCO_3$ solution, the organic layer was separated and the aqueous phase was extracted with $CHCl_3$ (3 × 30 mL). The combined organic layers were dried with (K_2CO_3), filtered, and concentrated to afford the crude product. Purification by flash chromatography gave the desired 1,2,3,4-tetrahydroisoquinoline derivative **3**.

4-Acetamido-1,2,3,4-tetrahydroisoquinoline (**3a**). (73%); mp 124–125°C (MeOH/Et_2O) (lit.[21] 124–126.5°C). IR (film): 3276, 3025, 2929, 1649, 1547 and 1289 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$): $\delta = 1.92$ (3H, s), 2.41 (1H, s), 3.02 (1H, dd, J 12.6 and 3.6 Hz), 3.10 (1H, dd, J 12.6 and 3.5 Hz),

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3.77 (1H, d, *J* 16.0 Hz), 3.90 (1H, d, *J* 16.0 Hz), 4.97 (1H, m) and 6.94–7.31 (5H, m). ^{13}C-NMR (50.3 MHz, $CDCl_3$): $\delta = 23.2$, 45.9, 47.9, 49.3, 126.2, 126.6, 127.3, 129.4, 134.9, 135.7 and 169.3. MS (EI): $m/z = 191$ ($M^+ + 1$, 2%), 132 (11), 131 (97), 130 (100), 119 (43), 118 (42) and 117 (22).

4-Acetamido-5,6,7,8-tetrahydroisoquinoline (**11a**). This compound was isolated (16%) in the hydrogenation of 4-acetamidoisoquinoline **8a**, mp 120–122°C (Et_2O) (lit.[21] 118–120.5°C). ^{1}H-NMR (200 MHz, $CDCl_3$): $\delta = 1.78$ (4H, m), 2.19 (3H, s), 2.59 (2H, m), 2.74 (2H, m), 7.85 (1H, br s), 8.12 (1H, s) and 8.51 (1H, s). MS (EI): $m/z = 190$ (M^+, 52), 149 (11), 148 (100), 147 (64), 133 (21) and 132 (12).

4-Benzamido-1,2,3,4-tetrahydroisoquinoline (**3b**). (87%); mp 138–139°C (Et_2O) (lit.[21] 138.5–140°C). ^{1}H-NMR (200 MHz, $CDCl_3$): $\delta = 2.25$ (1H, br s), 3.18 (2H, m), 3.97 (2H, m), 5.25 (1H, m), 7.00–7.49 (8H, m) and 7.74 (2H, d, *J* 7.6 Hz). ^{13}C-NMR (50.3 MHz, $CDCl_3$): $\delta = 46.4$, 48.2, 49.6, 126.2, 126.8, 127.0, 127.5, 128.4, 129.6, 131.4, 134.4, 135.0, 135.9, 166.4. MS (EI): $m/z = 252$ (M^+, 1%), 132 (10), 131 (100), 130 (79) and 105 (87).

4-Trifluoroacetamido-1,2,3,4-tetrahydroisoquinoline (**3c**). (83%); m.p. 119–120°C. IR (film): 3322, 1700, 1215 and 1184 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$): $\delta = 2.84$ (1H, br s), 3.15 (1H, dd, *J* 12.4 and 2.9 Hz), 3.25 (1H, dd, *J* 12.4 and 2.4 Hz) 3.88 (1H, d, *J* 15.6 Hz), 4. 00 (1H, d, *J* 15.6 Hz), 5.13 (1H, m), 7.08 (1H, m), 7.21–7.39 (3 H, m) and 7.64 (1H, m). ^{13}C-NMR (50.3 MHz, $CDCl_3$): $\delta = 46.6$, 47.5, 48.7, 116.0 (q, $J_{C\text{-}F}$ 287), 126.8, 127.1, 128.1, 129.6, 132.9, 135.1 and 156.3 (q, $J_{C\text{-}F}$ 35 Hz). MS (EI): $m/z = 244$ (M^+, 2%), 146 (54), 132 (15), 131 (100), 130 (87) and 118 (46). Anal. Calcd for $C_{11}H_{11}F_3N_2O$: C, 54.10; H, 4.54; N, 11.47. Found: C, 54.15; H, 4.72; N, 11.49.

4-Amino-1,2,3,4-tetrahydroisoquinoline (**3d**). A suspension of benzamide **3b** (77 mg, 0.31 mmol) in a 3M aqueous KOH solution (20 mL) was stirred at reflux temperature for 5 h. The resulting mixture was then diluted with brine and extracted thoroughly with $CHCl_3$ (6 × 25 mL). The organic extracts were dried (K_2CO_3), filtered and concentrated under reduced pressure to yield pure **3d** (99%). IR (film) 3329, 3214 and 1651 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$): $\delta = 1.78$ (3 H, br s), 2.96 (1H, dd, *J* 12.8 and 4.4 Hz), 3.15 (1H, dd, *J* 12.8 and 3.9 Hz), 3.88 (1H, m), 3.99 (2H, m) and 6.99–7.36 (4H, m). ^{13}C-NMR (50.3 MHz, $CDCl_3$): $\delta = 48.0$, 48.5, 52.1, 126.0, 126.5, 126.8, 128.6, 135.7 and 139.1. MS (EI): $m/z = 149$ ($M^+ + 1$, 4%), 148 (M^+, 25), 131 (63%), 130 (29) and 119 (100). HRMS: m/z calcd for $C_9H_{12}N_2$: 148.1000. Found 148.1009.

4-Cyanoisoquinoline (**9**). 4-Bromoisoquinoline (**1**, 5.10 g, 24.3 mmol) was mixed thoroughly with CuCN (7.6 g, 84.9 mmol). The powdered mixture was heated at 225°C for 45 min. After cooling to room temperature, the

mixture was dissolved in a saturated aqueous $NaHCO_3$ solution (100 mL). A concentrated aqueous NH_4OH solution (15 mL) was added and the resulting mixture was stirred vigorously overnight, then it was extracted with EtOAc (3×200 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduce pressure to give nitrile **9** (3.4 g, 81%); mp 105–106°C (Hexane/Et_2O) (lit.[22] 104°C). ^{1}H-NMR (200 MHz, $CDCl_3$): $\delta = 7.81$ (1 H, m), 7.95 (1 H, m), 8.12 (1 H, d, *J* 8.0 Hz), 8.20 (1 H, d, *J* 8.0 Hz), 8.92 (1 H, s) and 9.44 (1 H, s).

Methyl 4-isoquinolinecarboxylate (**10**). Concd. H_2SO_4 (2 mL) was added to a solution of nitrile **9** (256 mg, 1.66 mmol) in MeOH (7 mL). The mixture was stirred at reflux temperature for 48 h. After completion of the reaction (monitored by GC-HPLC), the solvent was removed under reduced pressure, and the residue was taken up in EtOAc (25 mL), cooled to 0°C and made alkaline (pH = 8) with a saturated aqueous $NaHCO_3$ solution. The phases were separated and the aqueous layer was extracted with AcOEt (3×25 mL). The combined organic layers were dried (Na_2CO_3–Na_2SO_4), filtered and concentrated to afford ester **10** (216 mg, 70%). mp 82–83°C (lit.[22] 81°C). ^{1}H-NMR (200 MHz, $CDCl_3$): $\delta = 4.04$ (3H, s), 7.69 (1H, m), 7.85 (1H, m), 8.04 (1H, d, *J* 8.4), 8.95 (1H, d, *J* 9.1), 9.19 (1H, s) and 9.38 (1H, s). ^{13}C-NMR (50.3 MHz, $CDCl_3$): $\delta = 52.4$, 120.4, 125.0, 127.6, 127.8, 128.2, 132.2, 133.8, 146.7, 156.9, 166.8.MS (EI): $m/z = 188$ ($M^+ + 1$, 10%), 187 (M^+, 80%), 156 (100%) and 128 (97).

Methyl 1,2,3,4-tetrahydroisoquinoline-4-carboxylate (**4a**). Following the general procedure for the hydrogenation of isoquinoline derivatives, (reaction time 24 h), the reduced ester **4a** (139 mg, 88%) was obtained in essentially pure form as a yellow oil and was used without further purification in the next step. ^{1}H-NMR (200 MHz, $CDCl_3$): $\delta = 2.27$ (1H, br s), 3.08 (1H, dd, *J*13.6 and 4.8Hz), 3.47 (1H, d, *J* 13.6 Hz), 3.63 (1H, m), 3.68 (3H, s), 3.98 (2H, m) and 7.00–7.26 (4H, m).

1,2,3,4-Tetrahydroisoquinoline-4-carboxylic acid (**4b**). A suspension of aminoester **4a** (405 mg, 2.12 mmol) in water (10 mL) was stirred at reflux temperature for 24 h. The mixture was cooled to room temperature and then was washed with Et_2O (3×25 mL). The aqueous phase was evaporated to dryness to afford aminoacid **4b** as a white solid (338 mg, 90%); mp. 237–238°C. IR (film): 3063, 3016, 1584 and 1390 cm^{-1}. ^{1}H-NMR (200 MHz, D_2O): $\delta = 3.24$ (1 H, dd, *J* 12.4 and 4.4 Hz), 3.53 (1H, dd, *J* 12.4 and 3.9 Hz), 3.68 (1H, m), 4.20 (2H, m) and 7.02–7.26 (4H, m). ^{13}C-NMR (50.3 MHz, D_2O): $\delta = 41.2$, 41.8, 41.9, 124.6, 125.1, 125.5, 125.9, 126.3, 128.8 and 176.9. MS (EI): $m/z = 179$ ($M^+ + 2$, 1%), 178 ($M^+ + 1$, 5%), 177 (M^+, 42%), 176 (47), 160 (12), 148 (12), 132 (37), 131 (48) and 130 (100). Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.28; N, 7.90. Found: C, 67.63; H, 6.42; N, 7.73.

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CONCLUSIONS

A unified synthesis for several 4-substitued-1,2,3,4-tetrahydroisoquinolines has been developed, involving the use of a single starting material (a commercially available isoquinoline) in a fast (3–4 steps), flexible and practical (multigram) protocol. The key reactions involved are the copper-promoted SNAr and the catalytic hydrogenation upon the 4-substituted isoquinolines to furnish the synthetic targets **2**, **3** and **4** in good yields. Although the prepared compounds are racemates, their resolution (if convenient or desirable at a later stage) may be routinely addressed by chiral HPLC or derivatization (being amines or carboxylic acids).

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