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Tetrahedron
Tetrahedron 62 (2006) 6869–6875

Synthesis of substituted 5-aminomethyl tetrahydro-isoquinolines and dihydro-isoindoles

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Received 2 November 2005; revised 18 April 2006; accepted 28 April 2006
Available online 26 May 2006

Abstract—The synthesis of ten substituted aminomethylene tetrahydro-isoquinolines is described, proceeding in eight steps from 5-hydroxyisoquinoline via reductive amination of *N*-Boc tetrahydro-isoquinoline 5-carboxaldehyde. Likewise, reductive amination was used to prepare four substituted dihydro-isoindoles from the corresponding aldehyde. The dihydro-isoindole ring system was conveniently accessed via a 2+2+2 cycloaddition reaction.
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1. Introduction

The introduction of conformational restraint is a frequently employed tactic for improving the potency and selectivity of biologically active compounds.[1] Di- or multi-functional compounds are useful components for building compound libraries to investigate structure–activity relationships rapidly. Hence difunctional compounds that possess a well-defined spatial relationship between the functional groups are particularly sought after as templates.[2] In connection with a programme to discover novel, selective α_1-adrenergic antagonists, we needed to prepare a range of tetrahydro-isoquinolines (**1**) and dihydro-isoindoles (**2**) (Fig. 1), bearing a variable basic substituent (NR^1R^2) attached to the ring system via a methylene group.

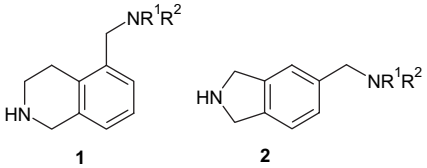

Figure 1.

The synthesis of **1** began with the reduction of commercially available 5-hydroxyisoquinoline (Scheme 1); hydrogenation over Adam's catalyst in acetic acid solvent[3] gave 5-hydroxy-tetrahydro-isoquinoline **3**. Treatment with an excess of Boc-anhydride afforded a mixture of *N*-Boc and *N*,*O*-diprotected products, which were not separated but exposed to sodium hydroxide, resulting in the selective removal of the *O*-Boc group. Compound **4** was isolated in 84% yield. The phenol group was converted into the nitrile **5** by reaction with *N*-phenyl triflamide[4] followed by palladium-catalysed displacement of the triflate by zinc cyanide.[5] Reduction of the nitrile to the aldehyde **6** was best achieved using an excess of DIBAL-H in toluene at −78 °C,[6] followed by a careful quenching of the excess reagent using methanol, and a brief exposure to hydrochloric acid to hydrolyse the intermediate imine. The aldehyde was obtained in 88% yield without loss of the Boc group.

Aldehyde **6** was reacted with a variety of amines (see Table 1) in the presence of sodium triacetoxyborohydride,[7] followed by treatment of the products (**7a–j**) with a saturated solution of hydrogen chloride in dichloromethane to afford the deprotected amines (**1a–j**) as their hydrochlorides. In some cases (i.e., **7f–j**), the amine was more conveniently employed as its hydrochloride or trifluoroacetate salt; thus 1 equiv of triethylamine or sodium acetate was also added to the reductive amination to buffer the reaction mixture.

The amine used to prepare **7j**, 3-methoxy-3-methylazetidine, was made using the four-step route shown in Scheme 2.

Keywords: Tetrahydro-isoquinoline; Dihydro-isoindole; Diamine; Reductive amination.
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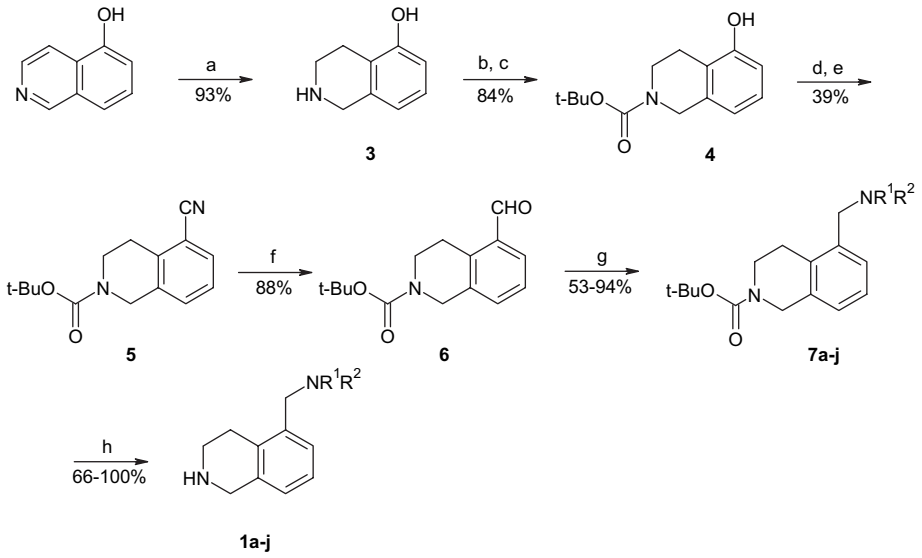
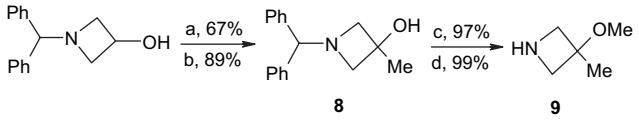
0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.04.095



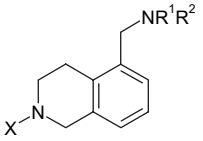
Scheme 1. Reagents and conditions: (a) H_2 (3 bar), PtO_2, HOAc, 16 h; (b) $(Boc)_2O$, NaOH, dioxane/water, 20 °C, 16 h; (c) 2 M NaOH (aq), MeOH/dioxane, 20 °C, 3 h; (d) $(Tf)_2NPh$, Et_3N, CH_2Cl_2, 0–20 °C, 16 h; (e) $Zn(CN)_2$ (1 equiv), 4 mol % $Pd(PPh_3)_4$, LiCl (1 equiv), DMF, 80 °C; (f) DIBAL-H (2.3 equiv), toluene, −78 °C, 2 h, then 1 M aq HCl, 0 °C, 20 min; (g) R^1R^2NH (1–1.5 equiv), MeCN, THF or CH_2Cl_2, 20 °C, 1–3 h, then $NaBH(OAc)_3$ (2.5 equiv), 18 h; (h) $HCl_{(g)}$, CH_2Cl_2, 20 °C, 1–2 h.

Thus, commercially available *N*-benzhydrylazetidin-3-ol was oxidised to the ketone using DMSO and pyridine–sulfur trioxide complex[12] and then treated with methylmagnesium bromide to afford **8**. Alkylation of the alcohol and removal of the benzhydryl group using chloroethyl chloroformate[13] gave **9** as the hydrochloride salt.

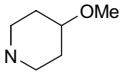
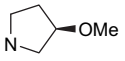
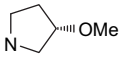


Scheme 2. (a) DMSO, Py–SO_3, 20 °C, 1.5 h; (b) MeMgBr (3 M in ether), THF, 0 °C, 2 h; (c) NaH, DMF, 0–20 °C, 2 h, then MeI, 0–20 °C, 2 h; (d) chloroethyl chloroformate, MeCN, reflux, 1 h, then MeOH, reflux, 2 h.

Table 1. Structures and yields of diamine products **7a–j** and **1a–j**



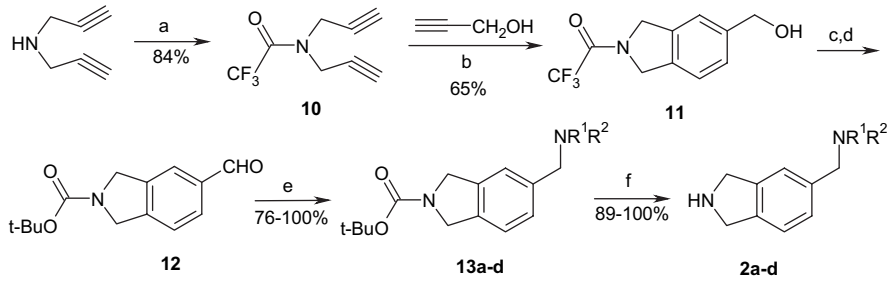
1: X = H; **7**: X = Boc

NR^1R^2	Compd (%yield)	Compd (%yield)	
NMe_2	**7a** (83)	**1a** (100)	
$NHCH_2CH_2OMe$	**7b** (81)	**1b** (100)	
$NMeCH_2CH_2OMe$	**7c** (64)	**1c** (90)	
	**7d** (77)	**1d** (99)	
	**7e** (66)	**1e** (66)	Ref. 8
	**7f** (94)	**1f** (99)	Ref. 9
	**7g** (89)	**1g** (99)	Ref. 10
	**7h** (53)	**1h** (84)	Ref. 11
	**7i** (65)	**1i** (100)	Ref. 10
	**7j** (74)	**1j** (100)	

For the synthesis of **2**, we utilised 2+2+2 cycloaddition chemistry to build up the isoindoline ring, as shown in Scheme 3.

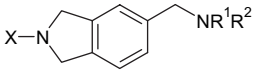
Thus, *N*,*N*-dipropynylamine was protected as its trifluoroacetyl derivative **10**, followed by reaction with 4 equiv of propynol in the presence of Wilkinson's catalyst to give hydroxymethylisoindoline **11**.[14] The trifluoroacetyl protecting group was chosen as it is easily removed under mild, basic conditions, however, we found that it was sometimes labile under reductive amination conditions. We therefore switched to the more robust Boc protection prior to oxidation using the modified Swern oxidation. The aldehyde **12** was obtained in good yield. Four amines were used in the reductive amination, and removal of the Boc group, as before, afforded the compounds shown in Table 2 (yields in parentheses).

In summary, we have developed efficient routes to a range of substituted tetrahydro-isoquinolines (**1**) and dihydro-isoindoles (**2**). These compounds were elaborated further to explore structure–activity relationships of α_1-adrenergic antagonists. Details of the synthesis of the target compounds, and their biological screening data, will be reported elsewhere.

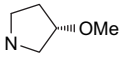


Scheme 3. (a) $(CF_3CO)_2O$, Et_3N, CH_2Cl_2, 0–20 °C; (b) 3 mol % $(PPh_3)_3RhCl$, EtOH, 0–20 °C, 17 h; (c) K_2CO_3, H_2O, MeOH, 20 °C, 30 min then $(Boc)_2O$, 20 °C, 6 h, 89%; (d) $(CF_3CO)_2O$, DMSO, CH_2Cl_2, −78 °C, then *i*-Pr_2NEt, warmed to 20 °C, 78%; (e) R^1R^2NH, HOAc, $NaBH(OAc)_3$, THF, 20 °C, 19 h; (f) $HCl_{(g)}$, CH_2Cl_2, 20 °C, 1 h.

Table 2. Structures and yields of diamine products **13a–d** and **2a–d**



2: X = H; **13**: X = Boc

NR^1R^2	Compd (%yield)	Compd (%yield)
	**13a** (99)	**2a** (99)
$NMeCH_2CH_2OMe$	**13b** (76)	**2b** (100)
	**13c** (100)	**2c** (99)
	**13d** (85)	**2d** (89)

2. Experimental

2.1. General

Melting points were determined using open glass capillary tubes and a Gallenkamp melting point apparatus and are uncorrected. Spectroscopic data were recorded on a Perkin–Elmer 983 (IR), Finnigan Mat. Navigator (LRMS, either positive (ES^+) or negative (ES^-) electrospray mode) and Varian Unity Inova (^1H NMR 300 or 400 MHz) instruments and are consistent with the assigned structures. Combustion analyses were performed by Exeter Analytical (UK) Limited, Uxbridge, Middlesex. Accurate mass determinations for molecular ions were obtained using a commercially available Apex II Fourier Transform Mass Spectrometer (Bruker Daltonics Inc., Billerica, MA, USA) equipped with a 4.7 T, passively shielded, superconducting magnet and an electrospray ionisation source (ESI), used in positive ion mode (Analytica of Branford, Branford, CT, USA) and calibrated using sodium trifluoroacetate. Reactions were performed under an atmosphere of dry nitrogen unless otherwise noted. Flash chromatography refers to column chromatography on silica gel (Kieselgel 60, 230–400 mesh, from E. Merck, Darmstadt). Kieselgel 60 F_{254} plates from E. Merck were used for TLC and compounds were visualised using UV light or 0.5% aqueous potassium permanganate solution.

2.1.1. 1,2,3,4-Tetrahydro-5-hydroxy-isoquinolinium acetate, 3.[3] A suspension of 5-isoquinolinol (24 g, 165 mmol) in acetic acid (250 mL) was hydrogenated over platinium dioxide (8 g), with overhead stirring, at 3 bar for 16 h at room temperature. The reaction mixture was decanted from the catalyst and the catalyst was thoroughly rinsed with methanol (1 L). The combined solutions were evaporated to dryness to give an oil (65 g). The residual oil was dissolved in methanol (200 mL) and diethyl ether was added. The solid, which precipitated, was collected by filtration, washed with diethyl ether and dried under vacuum to give **3** as an off-white solid (32.1 g, 93%). δ_H ($CDCl_3$, 300 MHz) 2.60 (m, 2H), 3.10 (m, 2H), 3.90 (m, 2H), 6.4 (d, *J* 8 Hz, 1H), 6.60 (d, *J* 8 Hz, 1H), 6.9 (t, *J* 8 Hz, 1H); LRMS: *m*/*z* (ES^+) 150 [MH^+].

2.1.2. *tert*-Butyl 3,4-dihydro-5-hydroxy-2(1*H*)-isoquinolinecarboxylate, 4. A solution of di-*tert*-butyl dicarbonate (66.75 g, 0.31 mol) in 1,4-dioxane (300 mL) was added to a mixture of **3** (32.0 g, 153 mmol) and 1 M aqueous sodium hydroxide (200 mL) and the resulting suspension stirred at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure and the residue partitioned between 1 M hydrochloric acid (300 mL) and dichloromethane (500 mL). The aqueous phase was re-extracted with dichloromethane (200 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give an orange oil. The crude product was dissolved in 1,4-dioxane (200 mL) and methanol (100 mL) followed by the addition of 2 N aqueous sodium hydroxide (150 mL) and the resulting cloudy mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure and the residue partitioned between ethyl acetate (600 mL) and water (200 mL). The organic phase was separated, washed with 2 N hydrochloric acid (200 mL), brine (250 mL) then dried ($MgSO_4$) and concentrated under reduced pressure to give a tan solid. The solid was suspended in dichloromethane (150 mL), then pentane (800 mL) was added and filtered to give **4** as a white solid (32.04 g, 84%). δ_H ($CDCl_3$, 300 MHz) 1.49 (s, 9H), 2.76 (t, *J* 6 Hz, 2H), 3.66 (t, *J* 6 Hz, 2H), 4.56 (s, 2H), 5.29 (br s, 1H), 6.63 (d, *J* 8 Hz, 1H), 6.71 (d, *J* 8 Hz, 1H), 7.05 (t, *J* 8 Hz, 1H); LRMS: *m*/*z* (ES^+) 272 [MNa^+]. Found: C, 67.30; H, 7.68; N, 5.61, $C_{14}H_{19}NO_3$ requires C, 67.45; H, 7.68; N, 5.62%.

2.1.3. *tert*-Butyl 5-cyano-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate, 5. Triethylamine (20.1 mL, 144 mmol) was added to a suspension of **4** (32.65 g, 131 mmol) in dichloromethane (400 mL). The mixture was cooled to 0 °C and *N*-phenyl-bis-(trifluoromethane)sulfonimide (51.46 g, 144 mmol) was added portionwise. The resulting brown solution

was allowed to warm to room temperature and stirred for 16 h. The reaction mixture was washed consecutively with water (200 mL), 0.5 M hydrochloric acid (200 mL), brine (250 mL) and then dried ($MgSO_4$) and concentrated under reduced pressure to give a brown oil. The crude product was purified by column chromatography on silica gel, eluting with a solvent gradient of *n*-pentane/diethyl ether (100:0–70:30). The product was co-evaporated with dichloromethane (2×100 mL) to give *tert*-butyl 5-[(trifluoromethanesulfonyl)oxy]-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate as a colourless gum (40.1 g, 80%). δ_H ($CDCl_3$, 300 MHz) 1.49 (s, 9H), 2.89 (t, *J* 5 Hz, 2H), 3.65 (t, *J* 5 Hz, 2H), 4.59 (s, 2H), 7.13 (m, 2H), 7.24 (m, 1H); LRMS: *m*/*z* (ES^+) 404 [MNa^+]. The triflate (20.0 g, 52 mmol) was dissolved in anhydrous DMF (120 mL) under nitrogen. Zinc cyanide (6.15 g, 52 mmol), lithium chloride (2.22 g, 52 mmol) and tetrakis(triphenylphosphine)palladium (0) (2.42 g, 2.1 mmol) were added and the mixture was heated at 110 °C for 8 h. The reaction mixture was concentrated under reduced pressure and the residue was partitioned between dichloromethane (500 mL) and saturated sodium bicarbonate solution (250 mL). The aqueous phase was re-extracted with dichloromethane (300 mL). The combined organic solutions were dried ($MgSO_4$) and concentrated under reduced pressure to give a golden oil. The crude product was purified by column chromatography on silica gel using *n*-pentane/ethyl acetate (90:10) as eluant. The product was co-evaporated with dichloromethane (2×100 mL) to give **5**, as a colourless oil (13.32 g, 49%). δ_H ($CDCl_3$, 300 MHz) 1.48 (s, 9H), 3.02 (t, *J* 6 Hz, 2H), 3.70 (t, *J* 6 Hz, 2H), 4.58 (s, 2H), 7.20 (t, *J* 7 Hz, 1H), 7.44 (d, *J* 7 Hz, 1H), 7.55 (d, *J* 7 Hz, 1H); LRMS: *m*/*z* (ES^+) 281 [MNa^+].

2.1.4. *tert*-Butyl 5-formyl-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate, 6. A solution of compound **5** (9.1 g, 35 mmol) in anhydrous toluene (100 mL) was cooled to −78 °C. Over 1 h, diisobutylaluminium hydride (80 mL of a 1 M solution in toluene, 80 mmol) was added dropwise keeping the internal temperature below −60 °C and the resulting mixture was stirred for 2 h at −78 °C. Methanol (20 mL) was pre-cooled to −78 °C and added dropwise to the reaction mixture keeping the internal temperature below −60 °C. Over 20 min, the reaction mixture was poured into 1 N hydrochloric acid (200 mL) that had been pre-cooled to 0 °C. The reaction mixture was extracted with ethyl acetate (3×400 mL) and the combined organic extracts were washed with brine (200 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The product was co-evaporated with dichloromethane (2×50 mL) to give **6**, as a yellow oil (8.14 g, 88%). δ_H (DMSO-d_6, 400 MHz) 1.40 (s, 9H), 3.19 (t, *J* 6 Hz, 2H), 3.55 (t, *J* 6 Hz, 2H), 4.55 (s, 2H), 7.40 (t, *J* 8 Hz, 2H), 7.47 (d, *J* 8 Hz, 1H), 7.70 (d, *J* 8 Hz, 1H), 10.16 (s, 1H); LRMS: *m*/*z* (ES^+) 284 [MNa^+].

2.1.5. 4-Methoxypiperidine hydrochloride. Sodium hydride (1.19 g, 60% in mineral oil, 29.7 mmol) was added portionwise to a cooled (10 °C) solution of *tert*-butyl 4-hydroxy-1-piperidinecarboxylate in anhydrous THF (80 mL) and the suspension was stirred at room temperature for 1 h. Iodomethane (1.85 mL, 29.7 mmol) was added and the reaction was stirred at 50 °C for 20 h. The mixture was diluted with water (50 mL), extracted with ethyl acetate (2×150 mL) and the combined organic extracts were washed with saturated sodium bicarbonate solution (50 mL), dried ($MgSO_4$) and evaporated under reduced pressure to afford *tert*-butyl 4-methoxy-1-piperidinecarboxylate as a golden oil, 5.24 g. ^1H NMR δ_H ($CDCl_3$, 400 MHz) 1.47 (s, 9H), 1.50 (m, 2H), 1.80 (m, 2H), 3.08 (m, 2H), 3.34 (m, 4H), 3.75 (m, 2H); LRMS: *m*/*z* (ES^+) 238 [MNa^+]. This material was dissolved in dichloromethane (100 mL), cooled to 0 °C and hydrogen chloride was bubbled through the solution. After being stirred for 1.5 h, the solution was purged with nitrogen and evaporated under reduced pressure to afford 4-methoxypiperidine hydrochloride as an off-white solid, 3.67 g, (82% over 2 steps).

δ_H (DMSO-d_6, 400 MHz) 1.87 (m, 2H), 1.99 (m, 2H), 3.10 (m, 2H), 3.28 (m, 2H), 3.36 (s, 3H), 3.54 (m, 1H); LRMS: *m*/*z* (ES^+) 231 [$2MH^+$].

2.1.6. *N*-Benzhydryl-3-methylazetidin-3-ol, 8. Triethylamine (49.4 mL, 0.36 mol) was added to a solution of *N*-benzhydrylazetidin-3-ol (10 g, 36 mmol) in DMSO (50 mL). A solution of sulfur trioxide–pyridine complex (36 g, 0.22mol) in DMSO (110 mL) was added dropwise and the resulting yellow solution was stirred at room temperature for 1.5 h. The reaction was poured onto ice-water (300 mL) and extracted with ethyl acetate (2×300 mL). The combined organic extracts were washed with brine (3×200 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using cyclohexane/ethyl acetate (8:2) as eluant to give *N*-benzhydrylazetidin-3-one as a white solid (5.77 g, 67%).

δ_H ($CDCl_3$, 300 MHz) 3.99 (s, 4H), 4.58 (s, 1H), 7.2 (m, 2H), 7.25 (t, *J* 8 Hz, 4H), 7.47 (d, *J* 8 Hz, 4H); LRMS: *m*/*z* (ES^+) 238 [MH^+], 260 [MNa^+]. The azetidinone (5.77 g, 24.3 mmol) was dissolved in THF (60 mL) and cooled to 0 °C. Methylmagnesium bromide (16.2 mL, 48.7 mmol) was added dropwise and stirring continued at 0 °C for 2 h. The reaction was carefully quenched with saturated ammonium chloride (100 mL) and extracted with ethyl acetate (150 mL). The organic solution was washed with brine (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using cyclohexane/ethyl acetate (8:2) as eluant to give *N*-benzhydryl-3-methylazetidin-3-ol[15] as a golden oil (5.48 g, 89%). δ_H ($CDCl_3$, 300 MHz) 1.52 (s, 3H), 2.97 (d, *J* 8 Hz, 2H), 3.18 (d, *J* 8 Hz, 2H), 4.35 (s, 1H), 7.17 (t, *J* 6 Hz, 2H), 7.26 (t, *J* 6 Hz, 4H), 7.40 (d, *J* 6 Hz, 4H); LRMS: *m*/*z* (ES^+) 254 [MH^+], 276 [MNa^+].

2.1.7. 3-Methoxy-3-methylazetidine hydrochloride, 9. Azetidinol **8** (3.46 g, 13 mmol) was dissolved in DMF (50 mL) and cooled to 0 °C. Sodium hydride (820 mg, 60% in mineral oil, 20.5 mmol) was added portionwise and the suspension was stirred for 2 h. The mixture was re-cooled to 0 °C and a solution of iodomethane (1.06 mL, 17 mmol) in DMF (10 mL) was added dropwise. After being stirred for 3 h, the mixture was diluted with ethyl acetate (125 mL) and washed with water (2×80 mL). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using cyclohexane/ethyl acetate (8:2) as eluant to give *N*-benzhydryl-3-methoxy-3-methylazetidine as a

golden oil (3.55 g, 97%). δ_H ($CDCl_3$, 300 MHz) 1.49 (s, 3H), 3.01 (d, *J* 9 Hz, 2H), 3.10 (d, *J* 9 Hz, 2H), 3.18 (s, 3H), 4.38 (s, 1H), 7.17 (t, *J* 9 Hz, 2H), 7.25 (t, *J* 9 Hz, 4H), 7.41 (d, *J* 9 Hz, 4H); LRMS: *m/z* (ES^+) 268 [MH^+], 290 [MNa^+]. The benzhydryl-protected compound (500 mg, 1.87 mmol) was dissolved in acetonitrile (10 mL) and cooled to 0 °C. 1-Chloroethyl chloroformate (0.26 mL, 2.43 mmol) was added and the reaction was refluxed for 1 h. The mixture was concentrated under reduced pressure, re-dissolved in methanol (10 mL) and refluxed for 2 h. The mixture was concentrated under reduced pressure and the residue was dissolved in water (10 mL), washed with cyclohexane (2×20 mL), the aqueous was concentrated under reduced pressure and co-evaporated with ethanol (50 mL) then dichloromethane (50 mL) to give **9** as a white solid (256 mg, 100%). δ_H (DMSO-d_6, 400 MHz) 1.42 (s, 3H), 3.15 (s, 3H), 3.70 (m, 2H), 3.85 (m, 2H), 9.20 (br s, 1H), 9.60 (br s, 1H).

2.1.8. (*N*,*N*-Dipropynyl)trifluoroacetamide, 10. A solution of trifluoroacetic anhydride (8.40 g, 40 mmol) in anhydrous dichloromethane (15 mL) was added dropwise to a stirred solution of *N*,*N*-dipropargylamine (3.162 g, 34 mmol) and triethylamine (4.24 g, 42 mmol) in anhydrous dichloromethane (55 mL) at 4 °C. The resulting solution was allowed to warm to room temperature and stirred for 17 h. The mixture was poured into saturated aqueous sodium bicarbonate (100 mL) and extracted with dichloromethane (75 mL and 50 mL). The combined organic solutions were washed with water (75 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography, (gradient elution with hexane/ethyl acetate) to give **10** (5.4 g, 84%). δ_H ($CDCl_3$, 300 MHz) signals doubled due to rotational isomerism 2.14, 2.18 (t, *J* 3 Hz, 1H), 4.17, 4.20 (d, *J* 3 Hz, 2H); IR ν_{max} (film) 3300, 2130, 1700 cm^{-1}. $C_8H_6F_3NO$ requires C, 50.80; H, 3.20; N, 7.41%, found C, 50.78; H, 3.21; N, 7.24%.

2.1.9. 2,3-Dihydro-5-hydroxymethyl-2-trifluoroacetyl(1*H*)isoindole, 11. Propargyl alcohol (4.28 g, 76 mmol) was added dropwise to a solution of **10** (3.61 g, 19.1 mmol) in ethanol (80 mL) at 0 °C. Tris(triphenylphosphine)rhodium (I) chloride (535 mg, 0.579 mmol) was added in one portion and the reaction was stirred at room temperature for 17 h. The mixture was concentrated under reduced pressure and the crude product was purified by flash chromatography using pentane/ethyl acetate (2:1) as eluant to give **11** as an off-white solid (2.73 g, 58%), mp 83–86 °C. δ_H ($CDCl_3$, 300 MHz) 1.80 (br s, 1H, exchanges with D_2O), 4.70 (s, 2H), 4.90 (s, 2H), 5.05 (s, 2H), 7.2–7.4 (m, 3H); LRMS (TSP): *m/z* 262 [MNH_4^+]; IR ν_{max} (film) 3350, 3250, 1700 cm^{-1}. Found: C, 53.76; H, 4.07; N, 5.63, $C_{11}H_{10}F_3NO_2$ requires C, 53.88; H, 4.11; N, 5.71%

2.1.10. 2,3-Dihydro-5-formyl-2-*tert*-butoxycarbonyl(1*H*)isoindole, 12. 2,3-Dihydro-5-hydroxymethyl-2-trifluoroacetyl(1*H*)isoindole (2.73 g, 11.1 mmol) was dissolved in methanol (80 mL) and a solution of potassium carbonate (12.27 g, 88.8 mmol) in water (32 mL) was added. The cloudy mixture was stirred at room temperature for 30 min before adding di-*tert*-butyldicarbonate (4.85 g, 22.2 mmol) and stirring for 6 h. The reaction mixture was diluted with ethyl acetate (200 mL), washed with water (2×100 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give 2,3-dihydro-5-hydroxymethyl-2-*tert*-butoxycarbonyl(1*H*)isoindole as an off-white solid (2.49 g, 89%). δ_H ($CDCl_3$, 300 MHz) 1.51 (s, 9H), 4.6–4.70 (m, 6H), 7.15–7.3 (m, 3H); APCI: *m/z* 250 (MH^+).

Dimethylsulfoxide (2.28 mL, 32.2 mmol) in dichloromethane (6 mL) was added dropwise to a suspension of trifluoroacetic anhydride (3.42 mL, 24.2 mmol) in dichloromethane (60 mL) under nitrogen at −78 °C. After 10 min, a solution of 2,3-dihydro-5-hydroxymethyl-2-*tert*-butoxycarbonyl(1*H*)isoindole (4.0 g, 16.1 mmol) in dichloromethane (20 mL) was added dropwise to the mixture for over 25 min. After a further 20 min at −78 °C, *N*,*N*-diisopropylethylamine (14.02 mL, 80.5 mmol) was added dropwise for over 15 min. The mixture was stirred at −78 °C for 20 min before allowing to warm up to room temperature. The light brown solution was diluted with diethyl ether (200 mL), washed sequentially with water (50 mL) and dilute citric acid (2×50 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give a light brown solid. The crude product was purified by flash chromatography using cyclohexane/ethyl acetate (3:1) as eluant to give **12** as a white solid (3.117 g, 78%), mp 118–119 °C. δ_H ($CDCl_3$, 300 MHz) 1.52 (s, 9H), 4.70–4.80 (m, 4H), 7.35–7.46 (m, 1H), 7.70–7.85 (m, 2H), 10.0 (s, 1H). Found: C, 67.91; H, 6.92; N, 5.70, $C_{14}H_{17}NO_3$ requires C, 68.00; H, 6.93; N, 5.66%.

2.2. Reductive aminations: general method

A mixture of aldehyde (**6** or **12**) (1.05 mmol), the required amine (1.0 equiv) and acetic acid (1.15 equiv) in THF (10 mL) was stirred at room temperature for 0.5 h. In some cases the amine was used as its hydrochloride salt; thus anhydrous sodium acetate (1.0 mmol) was also added to buffer the mixture. Sodium triacetoxyborohydride (2.5 equiv) was added and the mixture stirred at room temperature for 18 h. The mixture was diluted with ethyl acetate and basified to pH 11 using concentrated aqueous ammonia. The layers were separated, the aqueous phase extracted with ethyl acetate and the combined organic solutions dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using dichloromethane/methanol/concentrated aqueous ammonia (typically between 97:3:0 and 90:10:1) as eluant to afford **7a–j** and **13a–d** as oils. Yields are shown in Tables 1 and 2.

Spectroscopic data for the amines **7a–j** and **13a–d** are given below.

Amine **7a**: colourless oil; δ_H ($CDCl_3$, 400 MHz) 1.5 (s, 9H), 2.2 (s, 6H), 2.90 (t, *J* 6 Hz, 2H), 3.35 (s, 2H), 3.62 (t, *J* 6 Hz, 2H), 4.55 (s, 2H), 7.00 (m, 1H), 7.10 (m, 2H); LRMS: *m/z* (ES^+) 291 [MH^+], 313 [MNa^+].

Amine **7b**: colourless oil; δ_H ($CDCl_3$, 400 MHz) 1.47 (s, 9H), 2.8–2.9 (m, 4H), 3.34 (s, 3H), 3.49 (t, *J* 6 Hz, 2H), 3.65 (t, *J* 6 Hz, 2H), 3.76 (s, 2H), 4.55 (s, 2H), 7.00 (d, *J* 6 Hz, 1H), 7.13 (t, *J* 6 Hz, 1H), 7.16 (d, *J* 6 Hz, 1H); LRMS: *m/z* (ES^+) 321 [MH^+], 343 [MNa^+].

Amine **7c**: colourless oil; δ_H ($CDCl_3$, 400 MHz) 1.48 (s, 9H), 2.21 (s, 3H), 2.59 (t, *J* 6 Hz, 2H), 2.91 (t, *J* 6 Hz, 2H), 3.31 (s,

2H), 3.47 (m, 5H), 3.62 (t, *J* 6 Hz, 2H), 4.55 (s, 2H), 6.99 (m, 1H), 7.10 (m, 2H); LRMS: *m/z* (ES^+) 335 [MH^+], 357 [MNa^+]. Found: C, 66.74; H, 8.88; N, 8.20, $C_{19}H_{30}N_2O_3\cdot 0.4H_2O$ requires C, 66.79; H, 9.09; N, 8.20%.

Amine **7d**: colourless oil; δ_H ($CDCl_3$, 400 MHz) 1.50 (s, 9H), 2.43 (m, 4H), 2.93 (t, *J* 5 Hz, 2H), 3.44 (s, 2H), 3.67 (m, 6H), 4.58 (s, 2H), 7.03 (m, 1H), 7.12 (m, 2H); LRMS: *m/z* (ES^+) 333 [MH^+], 355 [MNa^+].

Amine **7e**: colourless oil; δ_H ($CDCl_3$, 400 MHz) 1.47 (s, 9H), 1.56 (m, 2H), 1.84 (br, 2H), 2.13 (m, 2H), 2.68 (br, 2H), 2.90 (t, *J* 6 Hz, 2H), 3.20 (m, 1H), 3.31 (s, 3H), 3.41 (s, 2H), 3.62 (m, 2H), 4.56 (s, 2H), 7.00 (m, 1H), 7.10 (m, 2H). Found: C, 69.64; H, 8.94; N, 7.72, $C_{21}H_{32}N_2O_3$ requires C, 66.97; H, 8.95; N, 7.77%.

Amine **7f**: pale pink oil; δ_H ($CDCl_3$, 400 MHz) 1.48 (s, 9H), 1.77 (m, 1H), 2.02 (m, 1H), 2.5 (m, 2H), 2.61 (m, 1H), 2.77 (m, 1H), 2.88 (t, *J* 6 Hz, 2H), 3.25 (s, 3H), 3.56 (s, 2H), 3.62 (t, *J* 6 Hz, 2H), 3.90 (m, 1H), 4.55 (s, 2H), 6.99 (d, *J* 8 Hz, 1H), 7.08–7.18 (m, 2H); LRMS: *m/z* (ES^+) 347 [MH^+]. Found: C, 68.68; H, 8.73; N, 8.04, $C_{20}H_{30}N_2O_3\cdot 0.16H_2O$ requires C, 68.76; H, 8.74; N, 8.02%.

Amine **7g**: colourless oil; δ_H ($CDCl_3$, 400 MHz) 1.48 (s, 9H), 1.76 (m, 1H), 2.02 (m, 1H), 2.5 (m, 2H), 2.61 (m, 1H), 2.77 (m, 1H), 2.88 (t, *J* 6 Hz, 2H), 3.25 (s, 3H), 3.56 (s, 2H), 3.62 (t, *J* 6 Hz, 2H), 3.90 (m, 1H), 4.55 (s, 2H), 6.99 (d, 1H), 7.10 (t, *J* 8 Hz, 1H), 7.16 (d, *J* 8 Hz, 1H); LRMS: *m/z* (ES^+) 347 [MH^+], 369 [MNa^+]. Found: C, 68.71; H, 8.71; N, 7.86, $C_{20}H_{30}N_2O_3\cdot 0.1H_2O$ requires C, 68.97; H, 8.74; N, 8.04%.

Amine **7h**: oil; δ_H ($CDCl_3$, 400 MHz) 1.48 (s, 9H), 1.69 (d, *J* 10 Hz, 1H), 1.85 (d, *J* 10 Hz, 1H), 2.57 (d, *J* 10 Hz, 1H), 2.83 (d, *J* 10 Hz, 1H), 2.90 (t, *J* 6 Hz, 2H), 3.38 (s, 1H), 3.63 (t, *J* 6 Hz, 3H), 3.70 (d, *J* 2 Hz, 2H), 4.08 (d, *J* 6 Hz, 1H), 4.4 (s, 1H), 4.6 (s, 1H), 7.00 (d, *J* 6 Hz, 1H), 7.08–7.2 (m, 2H); LRMS: *m/z* (ES^+) 345 [MH^+], 367 [MNa^+].

Amine **7i**: colourless oil; δ_H ($CDCl_3$, 400 MHz) 1.45 (s, 9H), 2.81 (t, *J* 6 Hz, 2H), 2.95 (t, *J* 6 Hz, 2H), 3.22 (s, 3H), 3.60 (m, 6H), 4.01 (m, 1H), 4.58 (s, 2H), 7.00 (m, 1H), 7.13 (m, 2H); LRMS: *m/z* (ES^+) 333.3 [MH^+], 355 [MNa^+].

Amine **7j**: colourless oil; δ_H ($CDCl_3$, 400 MHz) 1.46 (s, 3H), 1.48 (s, 9H), 2.82 (t, *J* 6 Hz, 2H), 3.03 (d, *J* 6 Hz, 2H), 3.18 (s, 3H), 3.20 (m, 2H), 3.59 (s, 2H), 3.63 (t, *J* 6 Hz, 2H), 4.56 (s, 2H), 7.00 (br, 1H), 7.14 (m, 2H); LRMS: *m/z* (ES^+) 347 [MH^+], 369 [MNa^+].

Amine **13a**: white waxy solid; δ_H ($CDCl_3$, 400 MHz) 1.48 (s, 9H), 2.42 (m, 4H), 3.48 (s, 2H), 3.68 (m, 4H), 4.65 (br, 4H), 7.20 (br m, 2H); LRMS: *m/z* (ES^+) 319 [MH^+], 341 [MNa^+].

Amine **13b**: yellow oil; δ_H ($CDCl_3$, 400 MHz) 1.48 (s, 9H), 2.24 (s, 3H), 2.39 (t, *J* 6 Hz, 2H), 3.31 (s, 2H), 3.49 (t, *J* 6 Hz, 2H), 3.53 (s, 3H), 4.55–4.7 (br s, 4H), 7.06–7.35 (br m, 3H); LRMS: *m/z* (ES^+) 321 [MH^+], 343 [MNa^+].

Amine **13c**: colourless oil; δ_H ($CDCl_3$, 400 MHz) 1.48 (s, 9H), 2.95 (t, *J* 6 Hz, 2H), 3.23 (s, 3H), 3.57 (t, *J* 6 Hz, 2H), 3.61 (s, 2H), 4.02 (m, 1H), 4.6–4.7 (br s, 4H), 7.1–7.2 (br, 3H); LRMS: *m/z* (ES^+) 319 [MH^+], 341 [MNa^+].

Amine **13d**: yellow oil; δ_H ($CDCl_3$, 400 MHz) 1.48 (s, 9H), 1.8 (br, 1H), 2.05 (m, 1H), 2.52 (br, 2H), 2.64 (m, 1H), 2.75 (br, 1H), 3.25 (s, 3H), 3.61 (s, 2H), 3.91 (br, 1H), 4.6–4.7 (br s, 4H), 7.1–7.25 (br, 3H); LRMS: *m/z* (ES^+) 333 [MH^+], 355 [MNa^+].

2.3. Deprotection of *N*-Boc derivatives (7a–j and 13a–d): general methods

Hydrogen chloride was bubbled through an ice-cooled solution of the Boc-protected amine (**7a–j** or **13a–d**) in dichloromethane (10–12 mL/g) for 20 min. The solution was then stirred for a further 30 min at room temperature and evaporated under reduced pressure to afford **1** or **2** (hydrochloride). Alternatively, a solution of the Boc-protected amine in dichloromethane (10–12 mL/g) was treated with an equal volume of trifluoroacetic acid and the solution stirred at room temperature for 2 h. Removal of the solvents under reduced pressure gave **1** or **2** (trifluoroacetate). Spectroscopic data for the amines **1a–j** and **2a–d** are given below.

Amine **1a**·HCl: colourless foam; δ_H (DMSO-d_6, 400 MHz) 2.50 (s, 6H), 3.15 (t, *J* 6 Hz, 2H), 3.35 (br, 2H), 4.26 (m, 4H), 7.30 (m, 2H), 7.55 (d, *J* 8 Hz, 1H), 9.55 (br, 2H); LRMS: *m/z* (ES^+) 191 [MH^+], 213 [MNa^+]. Found: C, 47.24; H, 7.14; N, 8.49, $C_{12}H_{18}N_2\cdot HCl\cdot H_2O\cdot CH_2Cl_2$ requires C, 47.36; H, 7.03; N, 8.50%.

Amine **1b**·2HCl: colourless foam; δ_H (DMSO-d_6, 400 MHz) 3.06 (t, *J* 6 Hz, 2H), 3.14 (t, *J* 6 Hz, 2H), 3.30 (s, 3H), 3.35 (t, *J* 6 Hz, 2H), 3.67 (t, *J* 6 Hz, 2H), 4.13 (s, 2H), 4.25 (s, 2H), 7.25 (d, *J* 6 Hz, 1H), 7.32 (t, *J* 6 Hz, 1H), 7.50 (d, *J* 6 Hz, 1H); LRMS: *m/z* (ES^+) 221 [MH^+], 243 [MNa^+]. Found: C, 50.1; H, 7.68; N, 8.78, $C_{13}H_{20}N_2O\cdot 2HCl\cdot H_2O$ requires C, 50.17; H, 7.77; N, 9.00%.

Amine **1c**: free base, pale yellow gum; δ_H ($CDCl_3$, 400 MHz) 2.23 (s, 3H), 2.6 (t, *J* 5 Hz, 2H), 2.82 (t, *J* 5 Hz, 2H), 3.16 (t, *J* 5 Hz, 2H), 3.32 (s, 3H), 3.47 (s, 2H), 3.50 (t, *J* 5 Hz, 2H), 4.01 (s, 2H), 6.9 (d, *J* 8 Hz, 1H), 7.06 (t, *J* 8 Hz, 1H), 7.13 (d, *J* 8 Hz, 1H); LRMS: *m/z* (ES^+) 235 [MH^+]. Found: C, 70.6; H, 9.56; N, 11.76, $C_{14}H_{22}N_2O\cdot 0.2H_2O$ requires C, 70.67; H, 9.49; N, 11.77%.

Amine **1d**·2HCl, colourless solid; δ_H (DMSO-d_6, 400 MHz) 3.20 (m, 4H), 3.37 (m, 2H), 3.62 (m, 2H), 3.90 (m, 4H), 4.22 (m, 2H), 4.32 (s, 2H), 7.30 (m, 2H), 7.62 (m, 1H), 9.58 (br s, 2H), 11.40 (br s, 1H); LRMS: *m/z* (ES^+) 233 [MH^+].

Amine **1e**: free base, gum; δ_H ($CDCl_3$, 400 MHz) 1.56 (m, 2H), 1.86 (br, 2H), 2.16 (dt, *J* 10 and 3 Hz, 2H), 2.69 (br, 2H), 2.82 (t, *J* 6 Hz, 2H), 3.15 (t, *J* 6 Hz, 2H), 3.20 (m, 1H), 3.32 (s, 3H), 3.39 (s, 2H), 4.01 (s, 2H), 6.90 (d, *J* 7 Hz, 1H), 7.03 (t, *J* 7 Hz, 1H), 7.10 (d, *J* 7 Hz, 1H). Found C, 72.88; H, 9.29; N, 10.69, $C_{16}H_{24}N_2O\cdot 0.3H_2O$ requires C, 72.80; H, 9.32; N, 10.61%.

Amine **1f**·2HCl: colourless foam; δ_H ($CDCl_3$, 400 MHz) 2.23 (br, 2H), 3.17 (br, 2H), 3.35 (s, 3H), 3.40 (br, 2H), 3.50 (br, 2H), 3.75 (m, 2H), 4.13 (br, 1H), 4.32 (br, 2H),

7.25 (d, *J* 8 Hz, 1H), 7.33 (t, *J* 8 Hz, 1H), 7.58 (d, *J* 8 Hz, 1H); LRMS: *m*/*z* (ES^+) 247 [MH^+].

Amine **1g**·2HCl: colourless foam; δ_H ($CDCl_3$, 400 MHz) 2.23 (br, 2H), 3.18 (br, 2H), 3.35 (s, 3H), 3.4 (br, 2H), 3.5 (br, 2H), 3.78 (m, 2H), 4.13 (br, 1H), 4.35 (br, 2H), 7.23 (d, *J* 6 Hz, 1H), 7.32 (t, *J* 6 Hz, 1H), 7.58 (d, *J* 6 Hz, 1H); LRMS: *m*/*z* (ES^+) 247 [MH^+].

Amine **1h**·2HCl: pale pink solid; δ_H (DMSO-d_6, 400 MHz), 2:1 mix of diastereomers due to protonation, 2.00 (m, 1H, major+minor), 2.43 (m, 1H, major+minor), 3.05–3.25 (m, 3H, major+minor), 3.4–3.6 (m, 3H, major+minor), 3.61 (d, *J* 8 Hz, 1H, major), 3.68 (d, *J* 11 Hz, 1H, minor), 4.2–4.5 (m, 6H, major+minor), 4.62 (s, 1H, minor), 4.68 (s, 1H, major), 7.30 (m, 2H, major+minor), 7.60 (d, *J* 8 Hz, 1H, minor), 7.70 (d, *J* 8 Hz, 1H, major), 9.60 (m, 2H, major+minor), 11.22 (br s, 1H, major), 11.56 (br s, 1H, minor); LRMS: *m*/*z* (ES^+) 245 [MH^+].

Amine **1i**·2HCl: colourless foam; δ_H (DMSO-d_6, 400 MHz) 3.01–3.40 (m, 7H), 3.90 (br s, 1H), 4.01 (br s, 1H), 4.22 (m, 6H), 4.40 (s, 2H), 7.28 (m, 2H), 7.43 (m, 1H), 9.40–9.56 (m, 2H); APCI: *m*/*z* (ES^+) 233 [MH^+].

Amine **1j**·HCl: yellow solid; δ_H (MeOH-d_4, 400 MHz), some signals doubled and broadened due to protonation, 1.53 and 1.55 (each br s, 3H total), 3.20 (br, 2H), 3.30 (s, 3H), 3.55 (t, *J* 6 Hz, 2H), 4.1–4.22 (br, 4H), 4.40 (s, 2H), 4.48 and 4.53 (each br s, 2H total), 7.35 (d, 1H), 7.40 (m, 2H); LRMS: *m*/*z* (ES^+) 247 [MH^+].

Amine **2a**·2HCl: colourless powder; δ_H (MeOH-d_4, 400 MHz) 3.13–3.38 (br m, 4H), 3.70–4.10 (br m, 4H), 4.38 (s, 2H), 4.67 (d, *J* 5 Hz, 4H), 7.54 (d, *J* 9 Hz, 1H), 7.59 (d, *J* 9 Hz, 1H), 7.66 (s, 1H); LRMS: *m*/*z* (ES^+) 219 [MH^+]; HRMS: found: 219.1493 (MH^+), $C_{13}H_{18}N_2O$ requires 219.1492.

Amine **2b**·2HCl: purple solid; δ_H (MeOH-d_4, 400 MHz) 2.84 (s, 3H), 3.34 (m, 1H), 3.40 (s, 3H), 3.60 (m, 1H), 3.73 (m, 2H), 4.34 (d, *J* 13 Hz, 1H), 4.50 (d, *J* 13 Hz, 1H), 4.66 (m, 4H), 7.55 (s, 2H), 7.6 (s, 1H); LRMS: *m*/*z* (ES^+) 221 [MH^+].

Amine **2c**·2HCl; colourless sticky foam; δ_H (MeOH-d_4, 400 MHz) 3.29 (s, 3H), 4.02 (m, 2H), 4.35 (m, 3H), 4.45 (s, 2H), 4.66 (m, 4H), 7.51 (s, 2H), 7.55 (s, 1H); LRMS: *m*/*z* (ES^+) 219 [MH^+]; HRMS: found: 219.1493660, $C_{13}H_{19}N_2O$ requires 219.1491897.

Amine **2d**·2HCl: pale purple foam; δ_H (MeOH-d_4, 400 MHz) 2.13 (m, 1H), 2.33 (m, 1H), 3.27 (s, 3H), 3.34 (m, 2H), 3.58 (m, 2H), 4.17 (br s, 1H), 4.44 (m, 2H), 4.66 (m, 4H), 7.52 (d, *J* 6 Hz, 1H), 7.61 (s, 1H); LRMS: *m*/*z* (ES^+) 233 [MH^+].

References and notes

1. Janecka, A.; Kruszynski, R. *Curr. Med. Chem.* **2005**, *12*, 471; Reissmann, S.; Imhof, D. *Curr. Med. Chem.* **2004**, *11*, 2823; Stefanic, P.; Dolenc, M. S. *Curr. Med. Chem.* **2004**, *11*, 945; Rich, D. H.; Homes, O. W. *Practice of Medicinal Chemistry*, 2nd ed.; Elsevier: London, 2003; pp 373–386.
2. Dolle, R. E. *J. Comb. Chem.* **2005**, *7*, 739; Dolle, R. E. *Mol. Divers.* **2000**, *4*, 39; Dolle, R. E. *J. Comb. Chem.* **2000**, *2*, 383; Dolle, R. E.; Nelson, K. H. *J. Comb. Chem.* **1999**, *1*, 235; Dolle, R. E. *Mol. Divers.* **1998**, *3*, 199.
3. Sall, D. J.; Grunwald, G. L. *J. Med. Chem.* **1987**, *30*, 2208; Durand, S.; Lusinchi, X.; Moreau, R. C. *Bull. Soc. Chim. Fr.* **1961**, 270.
4. Tilley, J. W.; Sarabu, R.; Wagner, R.; Mulkerins, K. *J. Org. Chem.* **1990**, *55*, 906.
5. Selnick, H. G.; Smith, G. R.; Tebben, A. J. *Synth. Commun.* **1995**, *25*, 3255.
6. Yoon, M. N.; Gyoung, Y. S. *J. Org. Chem.* **1985**, *50*, 2443.
7. Abdel-Magid, A. F.; Maryanoff, C. A. *Synlett* **1990**, 537.
8. Gio, P. Ger. Patent DE 2028179, 1970; *Chem. Abstr.* **1971**, *74*, 64215; details given in Section 2.
9. Chakravarty, S.; Dugar, S.; Lu, Q.; Qing, L.; Luedke, G. R.; Maventel, B. J.; Perumatam, J. J.; Tester, R. PCT WO 2004/022712; *Chem. Abstr.* **2004**, *140*, 270879.
10. Widmer, U. Eur. Patent 294599, 1988; *Chem. Abstr.* **1989**, *110*, 192839.
11. Flohr, A.; Jakob-Roetne, R.; Norcross, R. D.; Riemer, C. PCT WO 2003/049741; *Chem. Abstr.* **2003**, *139*, 53026.
12. Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.
13. Yang, B. V.; O'Rourke, D.; Li, J. *Synlett* **1993**, 195.
14. The *N*-acetyl analogue of **11** is described by Grigg, R.; Scott, R.; Stevenson, P. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1357.
15. Koike, H; Yoshimoto, M.; Nishino, H., Eur. Patent 266922, 1988; *Chem. Abstr.*, 109, 149361.