Abnormal products in the Bischler–Napieralski isoquinoline synthesis

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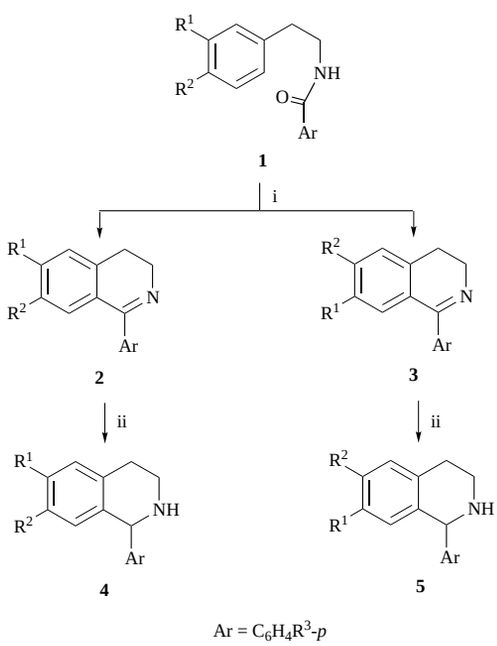
Reaction of *N*-[2-(4-methoxyphenyl)ethyl]benzamides with phosphorus pentoxide (and phosphoryl chloride) gives 7-methoxy-1-phenyl-3,4-dihydroisoquinolines (a normal Bischler–Napieralski reaction product) and 6-methoxy-1-phenyl-3,4-dihydroisoquinolines (an abnormal reaction product). The reaction mechanism is discussed.

The Bischler–Napieralski reaction[1] is of importance in isoquinoline syntheses. We noted that when *N*-[2-(4-methoxyphenyl)-ethyl]-4–methoxybenzamide **1a** (R^1 = H, R^2 = R^3 = OMe) was treated with a mixture of phosphoryl chloride and phosphorus pentoxide, typical Bischler–Napieralski reaction conditions, subsequent sodium borohydride reduction gave a 2:1 mixture of 7-methoxy-1-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline **4a** (normal product) and 6-methoxy-1-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline **5a** (abnormal product) respectively (Scheme 1). We have examined the effects of the



Scheme 1 *Reagents and conditions:* i, $POCl_3$, P_2O_5, xylene, 110–130 °C, 0.5–48 h; ii, $NaBH_4$, EtOH, RT, 1 h

reaction conditions and the substituents on the benzene ring on this abnormal reaction which gives rise to **5a**.

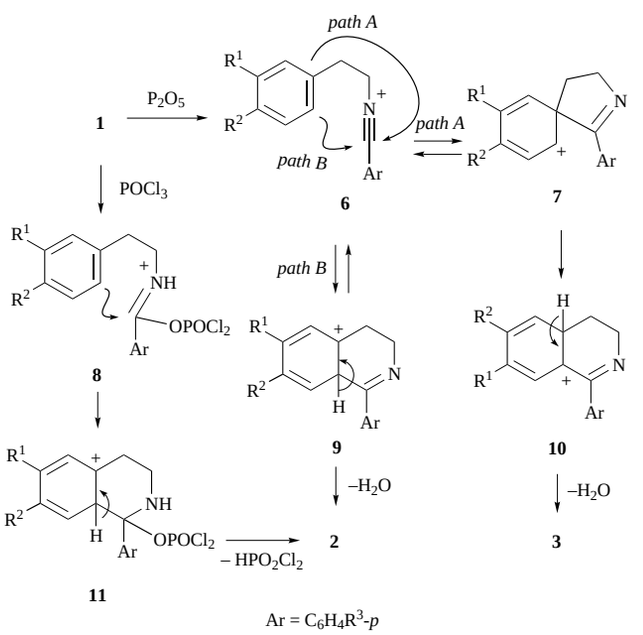
Results and discussion

When *N*-[2-(4-methoxyphenyl)ethyl]-4-methoxybenzamide **1a** was heated at reflux with phosphoryl chloride as in the synthesis of 6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline[2] **2e** and a 1-(4-methoxyphenyl) analogue[3] **2f** from *N*-[2-(3,4-dimethoxyphenyl)ethyl]benzamides **1e**,**f**, the yield of 7-methoxy-1-(4-methoxyphenyl)-3,4-dihydroisoquinoline **2a** was low (Table 1, compare entry 1 to 11 and 12). However, a mixture of **2a** and its constitutional isomer 6-methoxy-1-(4-methoxyphenyl)-3,4-dihydroisoquinoline **3a** was formed in a ratio of 37:63 when **1a** was treated with phosphorus pentoxide instead of phosphoryl chloride in xylene (entry 2). The use of a mixture of phosphoryl chloride and phosphorus pentoxide in a molar ratio of 2:1 resulted in a good yield and a higher ratio of **3a** (entry 3). Furthermore, refluxing in a mixture with a molar ratio of 9:1, which was made by adding phosphoryl chloride to a mixture of **1a** and phosphorus pentoxide, resulted in the selective formation of **3a** (entry 4). On the other hand, when a 9:1 mixture was made by adding a suspension of **1a** in phosphoryl chloride to phosphorus pentoxide, the ratio of **3a** was decreased (entry 5). Thus, contact between **1a** and phosphorus pentoxide should promote the formation of **3a**.

The effects of the substituents R^2 and R^3 were examined under the reaction conditions for entry 4 (entries 6–10). The reaction of *N*-[2-(4-methoxyphenyl)ethyl]benzamide **1b** also gave a mixture of 7-methoxy-1-phenyl-3,4-dihydroisoquinoline **2b** (normal product) and the 6-methoxy analogue **3b** (abnormal product) (entry 6). However, in the reports of Lantos *et al.*[4] and Minor *et al.*,[5] who worked with similar reaction conditions (entries 7 and 8) there is no mention of **3b** being formed; the reason for this difference in the results is unclear.

N-[2-(4-Methylphenyl)ethyl]-4-methoxybenzamide **1c** and the *N*-[2-(4-chlorophenyl)ethyl] analogue **1d** failed to form the corresponding abnormal product **3c**,**d**, even with prolonged heating of **1d** (entries 9, 10). Thus, the presence of a 4-methoxy group seems necessary in order to give formation of **3**.

In the reaction of **1** with phosphoryl chloride, cyclization to **2** may proceed *via* the dichlorophosphoric acid esters **8** (Scheme 2,



Scheme 2

Table 1 Bischler–Napieralski reaction of *N*-[2-(4-substituted phenyl)ethyl]-4-substituted benzamide **1**

					Reaction conditions			Total Yield	Product ratio [a]		
		R^1	R^2	R^3	Reagent (mol ratio)/solvent	Temp. (°C)	Time (h)	(%)	**2**	**3**	Ref.
1	**1a**	H	OMe	OMe	$POCl_3$/xylene	110	3	28	100	0	
2	**1a**	H	OMe	OMe	P_2O_5/xylene	130	3	18	37	63	
3	**1a**	H	OMe	OMe	$POCl_3/P_2O_5$(2:1)/xylene	130	3	64	16	84	
4	**1a**	H	OMe	OMe	$POCl_3/P_2O_5$(9:1) [b]	110	3	77	<5	>95	
5	**1a**	H	OMe	OMe	$POCl_3/P_2O_5$(9:1) [c]	110	3	50	67	33	
6	**1b**	H	OMe	H	$POCl_3/P_2O_5$(9:1) [b]	110	3	57	67	33	
7	**1b**	H	OMe	H	$POCl_3/P_2O_5$(1.6:1)/xylene	130	4	65	100	0	4
8	**1b**	H	OMe	H	$POCl_3/P_2O_5$(1.8:1)/xylene	130	6	5	100	0	5
9	**1c**	H	Me	OMe	$POCl_3/P_2O_5$(9:1) [b]	110	3	61	100	0	
10	**1d**	H	Cl	OMe	$POCl_3/P_2O_5$(9:1) [b]	110	48	19	100	0	
11	**1e**	OMe	OMe	H	$POCl_3$/toluene	110	1.5	85	100	0	2
12	**1f**	OMe	OMe	OMe	$POCl_3$/toluene	110	0.5	65	100	0	3

[a] The product ratios were determined by integration of the ^1H signals of the 500 MHz NMR spectrum. [b] $POCl_3$ was added to a mixture of **1a** and P_2O_5 after which the mixture was heated. [c] A suspension of **1a** in $POCl_3$ was added to P_2O_5 and the mixture was then heated.

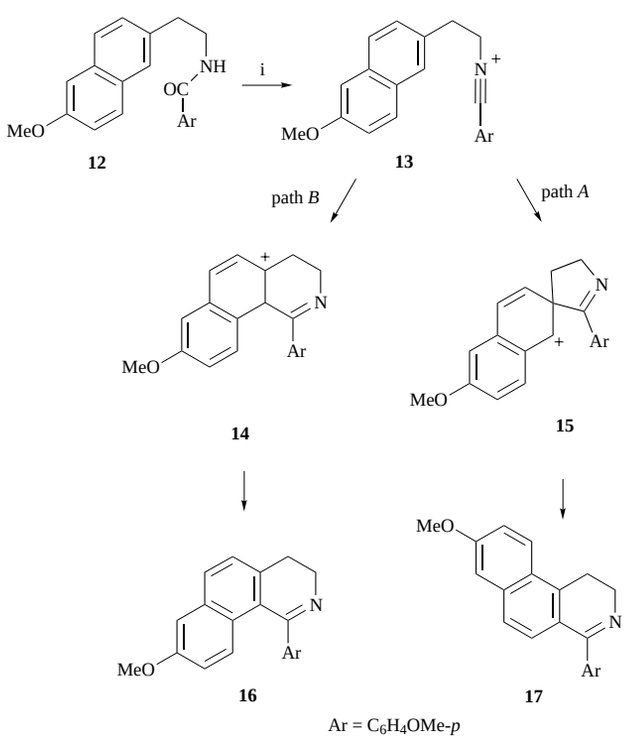
Table 2 Heats of formation (ΔH_f) of intermediates **6**, **7** and **9** and the energy increase [$\Delta E_A = \Delta H_f(\mathbf{7}) - \Delta H_f(\mathbf{6})$, $\Delta E_B = \Delta H_f(\mathbf{9}) - \Delta H_f(\mathbf{6})$] with PM3 (kcal mol^{-1})

	ΔH_f				
	6	**7**	**9**	ΔE_A	ΔE_B
a	162.2	173.7	178.4	11.5	16.2
b	200.3	212.8	217.3	12.5	17.0
c	188.4	210.7	204.3	22.3	15.9
d	193.0	215.0	211.3	22.0	18.3
e	166.4	178.0	175.6	11.6	9.2
f	125.1	140.7	130.0	15.6	4.9

1 ⟶ **8** ⟶ **11** ⟶ **2**).[6] However, in the presence of phosphorus pentoxide, the formation of a nitrilium intermediate **6** may become the main route.[7] Electrophilic attack by the nitrilium cation at C-2 of the phenyl group gives the intermediate **9** which is subsequently aromatized to **2** (path *B*, **1** ⟶ **6** ⟶ **9** ⟶ **2**), and attack at the C-1 carbon gives the spiro compound **7** which is isomerized to **3** *via* **10** (path *A*, **1** ⟶ **6** ⟶ **7** ⟶ **10** ⟶ **3**). When R^2 is a methoxy group and R^1 is hydrogen, path *A* becomes the main route because of the electron-donating effect of the methoxy group. The presence of a spiro intermediate has been reported in the Pictet–Spengler isoquinoline synthesis.[8]

We calculated the heats of formation (ΔH_f) of intermediates **6**, **7** and **9** with PM3,[9] and the energy increase (ΔE_A and ΔE_B) from ΔH_f(**6**) to ΔH_f(**7**) or ΔH_f(**9**) (Table 2). The formation energies ΔH_f(**7a**,**b**) are 4.5–4.7 kcal mol^{-1} lower than ΔH_f(**9a**,**b**), whereas ΔH_f(**7c**,**d**) are 3.7–6.4 kcal higher than ΔH_f(**9c**,**d**). This suggests that the conversion from **6a**,**b** into **7a**,**b** (path *A*) is easier than that into **9a**,**b** (path *B*) in the reaction of **1a**,**b**, while path *B* is easier than path *A* in the reaction of **1c**,**d**. Since the differences between ΔH_f(**7**) and ΔH_f(**9**) are small, both paths may occur in competition with each other. In the reaction of **1c**,**d**, however, conversion from **6c**,**d** into **7c**,**d** (path *A*) would be difficult because of the greater energy increase [ΔE_A (**c**,**d**) = *ca.* 22 kcal mol^{-1}] than in **1a**,**b** [ΔE_A (**a**,**b**) = *ca.* 12 kcal mol^{-1}]. Thus, path *A* and path *B* compete with each other in the reaction of **1a**,**b**, but not in that of **1c**,**d**. The cyclization of **6e**,**f** could proceed preferentially *via* path *B* because of the small energy increase [ΔE_B (**e**,**f**) = 4.9–9.2 kcal mol^{-1}]. Indeed, high yields of **2e**,**f** are obtained under mild reaction conditions (entries 11, 12).

To examine whether comparison of ΔH_f(**7**) and ΔH_f(**9**) or of ΔE_A and ΔE_B can really be used to predict the formation of abnormal products, we searched for compounds which should give abnormal Bischler–Napieralski reaction products. In the calculation for *N*-[2-(6-methoxy-2-naphthyl)ethyl]-4-methoxybenzamide **12**, the formation energies and the increase in energy



Scheme 3 *Reagents and conditions:* i, $POCl_3$, P_2O_5, 110 °C, 3 h

to the expected intermediates **13**, **14** and **15** are ΔH_f(**13**) = 177.8, ΔH_f(**14**) = 195.4 and ΔH_f(**15**) = 189.7 kcal mol^{-1}; ΔE_A = 11.9 (path *A*) and ΔE_B = 17.6 kcal mol^{-1} (path *B*) (Scheme 3). These values predict the formation of abnormal product **17**. The reaction of **12** with phosphoryl chloride and phosphorus pentoxide gave a mixture of 8-methoxy-1-(4-methoxyphenyl)-3,4-dihydrobenzo[*h*]isoquinoline **16** and 8-methoxy-4-(4-methoxyphenyl)-1,2-dihydrobenzo[*f*]isoquinoline **17** in a ratio of 49:51.

Experimental

Xylene was dried by distillation from Na. All melting points are uncorrected; *J* values are given in Hz. RT = room temperature.

N-[2-(4-Methoxyphenyl)ethyl]-4-methoxybenzamide 1a

A solution of 4-methoxybenzoyl chloride (5.97 g, 35.0 mmol) in $CHCl_3$ (15 cm^3) was added dropwise to a mixture of 2-(4-methoxyphenyl)ethylamine (4.56 g, 30.2 mmol), $CHCl_3$ (30 cm^3) and 20% aqueous K_2CO_3 (30 cm^3) at 2–4 °C. The mixture was stirred at RT for 3 h and then extracted with $CHCl_3$. The organic layer was washed with 1 M aqueous HCl and saturated

aqueous $NaHCO_3$, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was recrystallized from EtOH to give the *title amide* **1a** (7.36 g, 86%), mp 164–165 °C (Found: C, 71.6; H, 6.7; N, 4.9. $C_{17}H_{19}NO_3$ requires C, 71.6; H, 6.7; N, 4.9%); ν_{max}(Nujol)/cm^{-1} 3317 and 1637; δ_H(400 MHz; $CDCl_3$; Me_4Si) 2.86 (2 H, t, *J* 6.6), 3.66 (2 H, q, *J* 6.6), 3.80 (3 H, s), 3.83 (3 H, s), 6.04 (1 H, br s), 6.86 (2 H, d, *J* 8.8), 6.89 (2 H, d, *J* 9.0), 7.14 (2 H, d, *J* 8.8) and 7.66 (2 H, d, *J* 9.0).

***N*-[2-(4-Methylphenyl)ethyl]-4-methoxybenzamide 1c**

In a manner similar to that described above, a solution of 4-methoxybenzoyl chloride (3.43 g, 20.1 mmol) in $CHCl_3$ (10 cm^3) was added to a mixture of 2-(4-methylphenyl)ethylamine (1.90 g, 14.0 mmol), $CHCl_3$ (15 cm^3) and 20% aqueous K_2CO_3 (15 cm^3) and worked up to give the *title amide* **1c** (2.43 g, 64%), mp 114–115 °C (from EtOH) (Found: C, 75.6; H, 7.0; N, 5.3. $C_{17}H_{19}NO_2$ requires C, 75.8; H, 7.1; N, 5.2%); ν_{max}(Nujol)/cm^{-1} 3348 and 1639; δ_H(400 MHz; $CDCl_3$; Me_4Si) 2.33 (3 H, s), 2.88 (2 H, t, *J* 7.0), 3.67 (2 H, q, *J* 7.0), 3.83 (3 H, s), 6.10 (1 H, br s), 6.89 (2 H, d, *J* 8.8), 7.12 (4 H, s) and 7.66 (2 H, *J* 8.8).

***N*-[2-(4-Chlorophenyl)ethyl]-4-methoxybenzamide 1d**

Using the method described above, a solution of 4-methoxybenzoyl chloride (3.50 g, 20.5 mmol) in $CHCl_3$ (10 cm^3) was added to a mixture of 2-(4-chlorophenyl)ethylamine (2.03 g, 13.1 mmol), $CHCl_3$ (15 cm^3) and 20% aqueous K_2CO_3 (20 cm^3) and worked up to give the *title amide* **1d** (3.04 g, 80%), mp 168–170 °C (from EtOH) (Found: C, 66.3; H, 5.6; N, 4.9. $C_{16}H_{16}ClNO_2$ requires C, 66.3; H, 5.6; N, 4.8%); ν_{max}(Nujol)/cm^{-1} 3350 and 1637; δ_H(400 MHz; $CDCl_3$; Me_4Si) 2.89 (2 H, t, *J* 7.0), 3.66 (2 H, q, *J* 7.0), 3.83 (3 H, s), 6.12 (1 H, br s), 6.90 (2 H, d, *J* 9.2), 7.15 (2 H, d, *J* 8.5), 7.28 (2 H, d, *J* 8.5) and 7.66 (2 H, d, *J* 9.2).

Reaction of 1a with phosphoryl chloride (Table 1, entry 1)

To a solution of **1a** (10.61 g, 37.2 mmol) in xylene (100 cm^3) was added $POCl_3$ (160 g, 1.0 mol), and the mixture was heated at 110 °C for 3 h and then poured into ice–water. The mixture was washed with ethyl acetate, made alkaline with 20% aqueous NaOH and extracted with ethyl acetate. The organic layer was washed with water, dried ($MgSO_4$) and concentrated to give 7-methoxy-1-(4-methoxyphenyl)-3,4-dihydroisoquinoline **2a** (2.75 g, 28%), an oil; δ_H(500 MHz; $CDCl_3$; Me_4Si) 2.71 (2 H, t, *J* 7.3), 3.73 (3 H, s), 3.79 (2 H, t, *J* 7.3), 3.86 (3 H, s), 6.86 (1 H, d, *J* 2.4), 6.93 (1 H, dd, *J* 8.5 and 2.4), 6.94 (2 H, d, *J* 8.5), 7.18 (1 H, d, *J* 8.5) and 7.57 (2 H, d, *J* 8.5).

To a solution of **2a** (2.75 g, 10.3 mmol) in MeOH (14 cm^3) was added $NaBH_4$ (0.43 g, 11.4 mmol), and the mixture was stirred at RT for 1 h; it was then poured into water (60 cm^3) and extracted with ethyl acetate. The extract was washed with saturated brine, dried ($MgSO_4$) and concentrated under reduced pressure to give 7-methoxy-1-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline **4a** (1.58 g, 57%); mp 82–83 °C (from ethyl acetate) (Found: C, 76.0; H, 7.2; N, 5.2. $C_{17}H_{19}NO_2$ requires C, 75.8; H, 7.1; N, 5.2%); ν_{max}(KBr)/cm^{-1} 3256, 1608, 1506 and 1252; δ_H(400 MHz; $CDCl_3$; Me_4Si) 2.29 (1 H, br s), 2.69–3.26 (4 H, m), 3.64 (3 H, s), 3.79 (3 H, s), 5.03 (1 H, s), 6.29 (1 H, d, *J* 2.4), 6.72 (1 H, dd, *J* 2.4 and 8.5), 6.85 (2 H, d, *J* 8.5), 7.05 (1 H, d, *J* 8.5) and 7.18 (2 H, d, *J* 8.5).

Reaction of 1a with phosphorus pentoxide (Table 1, entry 2)

A mixture of **1a** (1.00 g, 3.5 mmol), P_2O_5 (4.19 g, 29.5 mmol) and xylene (15 cm^3) was heated at 130 °C for 3 h. The mixture was treated in a manner similar to that described above to give a mixture of **2a** and 6-methoxy-1-(4-methoxyphenyl)-3,4-dihydroisoquinoline **3a** (total 0.165 g, 18%, ratio 37:63). The structure of **3a** was determined by spectroscopic comparison with an authentic sample that had been prepared independently. The product ratio was determined from the proton ratios in an ^{1}H NMR spectrum of the mixture.

Reactions of 1a with phosphorus chloride and phosphorus pentoxide (Table 1, entry 3)

To a mixture of **1a** (1.00 g, 3.5 mmol), P_2O_5 (5.38 g, 37.9 mmol) and xylene (25 cm^3) was slowly added $POCl_3$ (10.43 g, 68.0 mmol). The mixture was allowed to react in a manner similar to that described above (entry 2) to give a mixture of **2a** and **3a** (total 0.60 g, 64%, ratio 16:84).

(Entry 4) To a mixture of **1a** (1.00 g, 3.5 mmol) and P_2O_5 (3.31 g, 23.4 mmol) was slowly added $POCl_3$ (32.9 g, 215 mmol). The mixture was heated at 110 °C for 3 h and then worked up to give a mixture of **2a** and **3a** (total 0.72 g, 77%, ratio <5:>95).

(Entry 5) A mixture of **1a** (6.20 g, 21.7 mmol) and $POCl_3$ (87.2 g, 569 mmol) was slowly added to P_2O_5 (18.0 g, 63 mmol). The mixture was allowed to react to give a mixture of **2a** and **3a** (total 2.90 g, 50%, ratio 67:33).

Reaction of *N*-[2-(4-methoxyphenyl)ethyl]benzamide[5] 1b with phosphoryl chloride and phosphorus pentoxide (Table 1, entry 6)

A mixture of compound **1b** (1.00 g, 3.9 mmol), $POCl_3$ (32.9 g, 215 mmol) and P_2O_5 (3.06 g, 21.5 mmol) was treated in a manner similar to that described above (entry 4) to give a mixture of 6-methoxy-1-phenyl-3,4-dihydroisoquinoline[5] **2b** and 5-methoxy-1-phenyl-3,4-dihydroisoquinoline[5] **3b** (total 0.525 g, 56%, ratio 67:33); δ_H(400 MHz; $CDCl_3$; Me_4Si) **2b**: 2.74 (2 H, t, *J* 7.3), 3.72 (3 H, s), 6.82 (1 H, d, *J* 2.6), 6.94 (1 H, dd, *J* 2.6 and 8.4) and 7.19 (1 H, d, *J* 8.4); **3b**: 2.79 (2 H, t, *J* 7.3), 3.85 (3 H, s), 6.74 (1 H, dd, *J* 2.6 and 8.4), 6.79 (1 H, d, *J* 2.6) and 7.21 (1 H, d, *J* 8.4); others 3.79–3.85 (2 H, m) and 7.40–7.62 (5 H, m).

To the mixture of **2b** and **3b** (483 mg, 2.0 mmol) in EtOH (20 cm^3) was added $NaBH_4$ (175 mg, 4.6 mmol). The mixture was stirred at RT for 1 h and then worked up in a manner similar to that described for the preparation of **4a** to give a mixture of 7-methoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline[5] **4b** and 6-methoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline[5] **5b** (total 473 mg, 97%, ratio 67:33); δ_H(400 MHz; $CDCl_3$; Me_4Si) **4b**: 3.63 (3 H, s), 5.06 (1 H, s), 6.29 (1 H, d, *J* 2.6), 6.73 (1 H, dd, *J* 2.6 and 8.4) and 7.06 (1 H, d, *J* 8.4); **5b**: 3.77 (3 H, s), 5.04 (1 H, s), 6.61 (1 H, dd, *J* 2.6 and 8.4), 6.66 (1 H, d, *J* 8.4) and 6.67 (1 H, d, *J* 2.6); others 2.02 (1 H, br s), 2.73–3.26 (4 H, m) and 7.24–7.34 (5 H, m). Isolation of **2b** and **3b**, and **4b** and **5b** was difficult because of insufficient separation on silica gel columns. The product ratios were determined from the proton ratios in the ^{1}H NMR spectra of the mixtures.

Reaction of 1c with phosphoryl chloride and phosphorus pentoxide (entry 9)

A mixture of compound **1c** (1.00 g, 3.7 mmol), $POCl_3$ (32.9 g, 215 mmol) and P_2O_5 (2.92 g, 23.4 mmol) was treated in a manner similar to that described for **1a** (entry 4) to give 7-methyl-1-(4-methoxyphenyl)-3,4-dihydroisoquinoline **2c** (0.57 g, 61%), an oil; δ_H(400 MHz; $CDCl_3$; Me_4Si) 2.30 (3 H, s), 2.74 (2 H, t, *J* 7.3), 3.79 (2 H, t, *J* 7.3), 3.86 (3 H, s), 6.95 (2 H, d, *J* 8.8), 7.11 (1 H, s), 7.15 (1 H, d, *J* 7.7), 7.20 (1 H, dd, *J* 1.1 and 7.7) and 7.56 (2 H, d, *J* 8.8).

To a solution of **2c** (552 mg, 2.2 mmol) in EtOH (20 cm^3) was added $NaBH_4$ (195 mg, 5.2 mmol), and the mixture allowed to react to give 7-methyl-1-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline **4c** (515 mg, 93%); δ_H(400 MHz; $CDCl_3$; Me_4Si) 2.18 (3 H, s), 2.30 (1 H, s), 2.78–3.23 (4 H, m), 3.80 (3 H, s), 5.03 (1 H, s), 6.57 (1 H, s), 6.86 (2 H, d, *J* 8.8), 6.95 (1 H, d, *J* 7.8), 7.02 (1 H, d, *J* 7.8) and 7.18 (2 H, d, *J* 8.8); hydrochloride **4c**·HCl; mp 195–197 °C (from EtOH) (Found: C, 70.4; H, 7.0; N, 4.5. $C_{17}H_{20}ClNO$ requires C, 70.5; H, 7.0; N, 4.8%); ν_{max}(KBr)/cm^{-1} 2758 and 1252; δ_H(500 MHz; $CDCl_3$; Me_4Si) 1.60 (2 H, s), 2.21 (3 H, s), 3.01–3.27 (4 H, m), 3.79 (3 H, s), 5.34 (1 H, s), 6.60 (1 H, s), 6.90 (2 H, d, *J* 8.5), 7.06 (2 H, s) and 7.31 (2 H, d, *J* 8.5).

Reaction of 1d with phosphoryl chloride and phosphorus pentoxide (entry 10)

To a mixture of **1d** (1.00 g, 3.5 mmol) and P_2O_5 (2.97 g, 20.9 mmol) was added $POCl_3$ (32.9 g, 215 mmol), and the mixture was heated at reflux for 48 h. Treatment of the reaction mixture in a manner similar to that described above gave 7-chloro-1-(4-methoxyphenyl)-3,4-dihydroisoquinoline **2d** (0.18 g, 19%); δ_H(500 MHz; $CDCl_3$; Me_4Si) 2.75 (2 H, t, *J* 7.3), 3.81 (2 H, t, *J* 7.3), 3.87 (3 H, s), 6.96 (2 H, d, *J* 8.6), 7.21 (1 H, d, *J* 7.9), 7.29 (1 H, d, *J* 2.4), 7.35 (1 H, dd, *J* 2.4 and 7.9) and 7.54 (2 H, d, *J* 8.6).

To a solution of **2d** (160 mg, 0.6 mmol) in EtOH (20 cm^3) was added $NaBH_4$ (51 mg, 1.4 mmol), and the mixture was stirred at RT for 1 h. Treatment of the reaction mixture gave 7-chloro-1-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline **4d** (142 mg, 88%); δ_H(400 MHz; $CDCl_3$; Me_4Si) 1.87 (1 H, br s), 2.78–3.26 (4 H, m), 3.81 (3 H, s), 4.99 (1 H, s), 6.74 (1 H, d, *J* 2.2), 6.87 (2 H, d, *J* 8.8), 7.06 (1 H, d, *J* 8.4), 7.10 (1 H, dd, *J* 2.2 and 8.4) and 7.16 (2 H, d, *J* 8.8); hydrochloride **4d**·HCl: mp 227–228 °C (from EtOH) (Found: C, 61.7; H, 5.5; N, 4.5. $C_{16}H_{17}Cl_2NO$ requires C, 61.95; H, 5.5; N, 4.5%); ν_{max}(KBr)/cm^{-1} 2758 and 1254; δ_H(500 MHz; $CDCl_3$; Me_4Si) 1.60 (2 H, s), 3.02–3.33 (4 H, m), 3.82 (3 H, s), 5.33 (1 H, s), 6.82 (1 H, d, *J* 2.4), 6.94 (2 H, d, *J* 8.4), 7.16 (1 H, d, *J* 8.5), 7.26 (1 H, dd, *J* 2.4 and 8.5) and 7.33 (2 H, d, *J* 8.4).

6-Methoxy-1-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline 5a

A mixture of *N*-[2-(3-methoxyphenyl)ethyl]-4–methoxybenzamide (2.02 g, 7.1 mmol), $POCl_3$ (74.0 g, 48 mmol) and P_2O_5 (5.0 g, 18 mmol) was heated at reflux for 3 h. The mixture was concentrated under reduced pressure and the residue was poured into ice–water. The mixture was washed with ethyl acetate, made alkaline with 20% aqueous NaOH and extracted with ethyl acetate. The extract was washed with water, dried ($MgSO_4$) and concentrated to give 6-methoxy-1-(4-methoxyphenyl)-3,4-dihydroisoquinoline **3a** (1.73 g, 92%), an oil; δ_H(500 MHz; $CDCl_3$; Me_4Si) 2.76 (2 H, t, *J* 7.3), 3.76–3.79 (2 H, m), 3.84 (3 H, s), 3.85 (3 H, s), 6.74 (1 H, dd, *J* 2.7 and 8.5), 6.79 (1 H, d, *J* 2.8), 6.92–6.95 (2 H, m), 7.24 (1 H, d, *J* 8.5) and 7.53–7.56 (2 H, m).

To a solution of **3a** (1.73 g, 6.5 mmol) in EtOH (20 cm^3) was added $NaBH_4$ (0.50 g, 13 mmol), and the mixture was stirred at RT for 1 h. Treatment of the reaction mixture in a manner similar to that for **4a** gave the *title compound* **5a** (1.70 g, 97%), mp 44–45 °C (from hexane) (Found: C, 75.9; H, 7.2; N, 5.3. $C_{17}H_{19}NO_2$ requires C, 75.8; H, 7.1; N, 5.2%); ν_{max}(KBr)/cm^{-1} 3300, 1610, 1510 and 1210; δ_H(400 MHz; $CDCl_3$; Me_4Si) 2.58 (1 H, br s), 2.77–2.84 (1 H, m), 2.99–3.09 (2 H, m), 3.20–3.27 (1 H, m), 3.77 (3 H, s), 3.79 (3 H, s), 5.01 (1 H, s), 6.61 (1 H, dd, *J* 2.6 and 8.4), 6.66 (1 H, d, *J* 2.6), 6.67 (1 H, d, *J* 8.4), 6.85 (2 H, d, *J* 8.8) and 7.18 (2 H, d, *J* 8.8).

***N*-[2-(6-Methoxynaphthyl)ethyl]-4-methoxybenzamide 12**

A solution of 2-cyanomethyl-6-methoxy-2-naphthalene[10] (197 mg, 1 mmol) in Et_2O (15 cm^3) was added dropwise to a mixture of $LiAlH_4$ (46 mg, 1.2 mmol), $AlCl_3$ (160 mg, 1.2 mmol) and Et_2O (20 cm^3). The mixture was heated at reflux for 3 h after which it was treated with water (10 cm^3) and 30 M KOH (20 cm^3) to quench the reaction, and extracted with Et_2O. The extract was washed with water, dried (K_2CO_3) and concentrated to give 2-[2-(6-methoxynaphthyl)]ethylamine (180 mg).

To a mixture of this amine (180 mg), $CHCl_3$ (10 cm^3) and 20% aqueous K_2CO_3 (10 cm^3) was added dropwise a solution of 4-methoxybenzoyl chloride (170 mg, 1 mmol) in $CHCl_3$ (10 cm^3), at 2–4 °C. The mixture was stirred at RT for 3 h and extracted with $CHCl_3$. The extract was washed with 1 M aqueous HCl and water, dried ($MgSO_4$) and concentrated. The residue was recrystallized from EtOH to give the *title amide* **12** (211 mg, 63%), mp 183–184 °C (Found: C, 75.0; H, 6.3; N, 4.3. $C_{21}H_{21}NO_3$ requires C, 75.2; H, 6.3; N, 4.2%); ν_{max}(KBr)/cm^{-1} 3378, 2961, 1645 and 1505; δ_H(500 MHz; $CDCl_3$; Me_4Si) 3.05 (2 H, t, *J* 6.7), 3.78 (2 H, q, *J* 6.7), 3.82 (3 H, s), 3.92 (3 H, s), 6.05 (1 H, br s), 6.87 (2 H, d, *J* 8.9), 7.12 (1 H, d, *J* 2.4), 7.15 (1 H, dd, *J* 2.4 and 8.9), 7.34 (1 H, dd, *J* 1.5 and 8.2), 7.61 (1 H, s), 7.64 (2 H, d, *J* 8.9), 7.68 (1 H, d, *J* 8.9) and 7.71 (1 H, d, *J* 8.2).

Reaction of 12 with phosphoryl chloride and phosphorus pentoxide

In a manner similar to that described for **1a** (entry 4), a mixture of compound **12** (1.00 g, 3.0 mmol), $POCl_3$ (32.9 g, 215 mmol) and P_2O_5 (2.84 g, 20.0 mmol) was heated at 110 °C for 3 h and then worked up to give a mixture of 8-methoxy-1-(4-methoxyphenyl)-3,4-dihydrobenzo[*h*]isoquinoline **16** and 8-methoxy-4-(4-methoxyphenyl)-1,2-dihydrobenzo[*f*]isoquinoline **17** (total 0.76 g, 81%, ratio 49:51), an oil; δ_H(500 MHz; $CDCl_3$; Me_4Si) **16**: 2.81 (2 H, t, *J* 6.7), 3.73 (2 H, t, *J* 6.7), 3.83 (3 H, s), 3.89 (3 H, s), 6.84 (1 H, dd, *J* 2.4 and 9.2), 6.85 (2 H, d, *J* 8.6), 7.12 (1 H, d, *J* 2.4), 7.28 (1 H, d, *J* 7.9), 7.37 (2 H, d, *J* 8.6), 7.39 (1 H, d, *J* 9.2) and 7.79 (1 H, d, *J* 7.9); **17**: 3.15 (2 H, t, *J* 7.9), 3.87 (3 H, s), 3.90 (2 H, t, *J* 7.9), 3.95 (3 H, s), 6.96 (2 H, d, *J* 9.2), 7.16 (1 H, d, *J* 3.1), 7.24 (1 H, dd, *J* 3.1 and 9.2), 7.38 (1 H, d, *J* 8.5), 7.57 (2 H, d, *J* 9.2), 7.60 (1 H, d, *J* 8.5) and 8.05 (1 H, d, *J* 9.2).

To a mixture of **16** and **17** (564 mg, 1.8 mmol) in EtOH (20 cm^3) was added $NaBH_4$ (172 mg, 4.6 mmol). The mixture was stirred at RT for 1 h after which it was worked up to give a mixture of 8-methoxy-1-(4-methoxyphenyl)-1,2,3,4-tetrahydrobenzo[*h*]isoquinoline **18** and 8-methoxy-4-(4-methoxyphenyl)-1,2,3,4-tetrahydrobenzo[*f*]isoquinoline **19** (total 483 mg, 85%, ratio 49:51), an oil; δ_H(500 MHz; $CDCl_3$; Me_4Si) **18**: 2.84–3.10 (4 H, m), 3.75 (3 H, s), 3.86 (3 H, s), 5.62 (1 H, s, 1-H), 6.78 (2 H, d, *J* 8.5, 3′-H), 6.93 (1 H, dd, *J* 3.1 and 9.2, 9-H), 7.05 (2 H, d, *J* 8.5, 2′-H), 7.09 (1 H, d, *J* 3.1, 7-H), 7.25 (1 H, d, *J* 8.5, 5-H or 6-H), 7.42 (1 H, d, *J* 9.2, 10-H) and 7.62 (1 H, d, *J* 8.5, 5-H or 6-H); **19**: 3.14–3.54 (4 H, m), 3.79 (3 H, s), 3.92 (3 H, s), 5.20 (1 H, s, 4-H), 6.84 (2 H, d, *J* 9.2, 3′-H), 6.88 (1 H, d, *J* 8.5, 5-H), 7.10 (1 H, d, *J* 2.4, 7-H), 7.17 (2 H, d, *J* 9.2, 2′-H), 7.20 (1 H, dd, *J* 2.4 and 9.2, 9-H), 7.45 (1 H, d, *J* 8.5, 6-H) and 7.91 (1 H, d, *J* 9.2, 10-H); **18**: upon irradiation at 5.62 ppm (1-H), 16% NOE enhancement at 7.42 ppm (10-H) and 14% NOE at 7.05 ppm (2′-H) were observed; **19**: under irradiation at 5.20 ppm (4-H), 7% NOE at 6.88 ppm (5-H) and 14% NOE at 7.17 ppm (2′-H) were observed; hydrochlorides **18**·HCl and **19**·HCl; mp 236–237 °C (Found: C, 70.8; H, 6.3; N, 3.7. $C_{21}H_{22}ClNO_2$ requires C, 70.9; H, 6.2; N, 3.9%); δ_H(500 MHz; $CDCl_3$; Me_4Si) **18**·HCl: 1.26 (2 H, s), 3.01–3.60 (4 H, m), 3.74 (3 H, s), 3.86 (3 H, s), 6.26 (1 H, s), 6.80 (2 H, d, *J* 9.2), 6.97 (1 H, dd, *J* 3.2 and 9.2), 7.10 (1 H, d, *J* 3.2), 7.19 (2 H, d, *J* 9.2), 7.24 (1 H, d, *J* 8.5), 7.29 (1 H, d, *J* 9.2) and 7.68 (1 H, d, *J* 8.5); **19**·HCl: 1.60 (2 H, s), 3.20–3.58 (4 H, m), 3.78 (3 H, s), 3.93 (3 H, s), 5.54 (1 H, s), 6.84 (1 H, d, *J* 9.2), 6.90 (2 H, d, *J* 8.5), 7.12 (1 H, d, *J* 2.4), 7.24 (1 H, dd, *J* 2.4 and 9.2), 7.32 (2 H, d, *J* 8.5), 7.54 (1 H, d, *J* 9.2) and 7.84 (1 H, d, *J* 9.2); ν_{max}(KBr)/cm^{-1} 3490, 2741 and 1252. Isolation of the products failed because of insufficient separation on silica gel columns. The product ratios were determined based on the proton ratios in the ^{1}H NMR spectra of the mixtures.

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