The asymmetric Bischler–Napieralski reaction: preparation of 1,3,4-trisubstituted 1,2,3,4-tetrahydroisoquinolines

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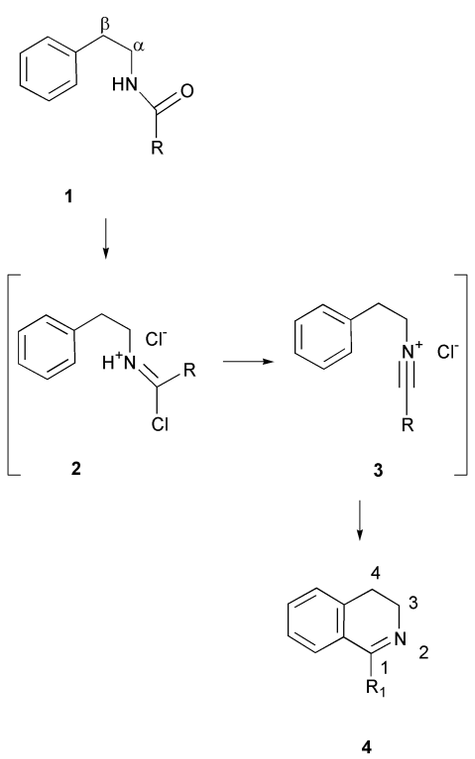
The Bischler–Napieralski reaction, which is used to prepare dihydroisoquinolines from phenylethylamides, is demonstrated by the reaction of (*S*)-1-alkyl-1,2-diphenylethylamides with $POCl_3$–P_2O_5. The reaction generated 3-alkyl-4-phenyl-1,2-dihydroisoquinolines with stereochemical selectivities of 80–91% de depending on the alkyl and the acetamide substituents. These are the first examples of the asymmetric Bischler–Napieralski reaction where cyclisation discriminates between two identical diastereotopic aryl groups. Reduction of the resultant dihydroisoquinoline products with $LiAlH_4$ generated the corresponding 1,2,3,4-tetrahydroisoquinolines in a stereoselective manner, carrying three stereogenic centres at C(1), C(3) and C(4).

Introduction

The Bischler–Napieralski reaction has been used widely and for many years for the preparation of isoquinoline derivatives.[1,2] The reaction involves the cyclodehydration of phenylethylamides **1** as illustrated in Scheme 1. Classically the reaction is carried out by the treatment of **1** with phosphorus oxychloride ($POCl_3$) and phosphorus pentaoxide (P_2O_5) in refluxing toluene. Imidoyl chlorides such as **2** have been identified[2] as reaction intermediates in the process and there is evidence to suggest that these reactions proceed *via* an intramolecular electrophilic aromatic substitution reaction on an intermediate nitrilium salt **3**[3] The reaction is extremely versatile and can be carried out with a variety of substituents on the aromatic ring, with α and β groups on the phenylethylamide and with various amides substituents.[4–7] We have recently developed[8] a synthetic method for the synthesis of a series of (*S*)-1-alkyl-2,2-diphenylethylamines, including **5** and **6**, from their corresponding amino acids (*S*)-alanine and (*S*)-valine. These compounds are prepared in enantiomerically pure forms and in either enantiomeric series depending on the amino acid enantiomer used at the outset. The availability of **5** and **6** presented an opportunity to explore the asymmetric Bischler–Napieralski reaction by their conversion to amides **7**–**9**. These amides possess a diphenylmethyl group. Each of the phenyl groups is diastereotopic and therefore there are two stereochemical courses available to the cyclisation, generating potentially two diastereoisomeric products for each amide substrate. In this paper we present the first study of such an asymmetric Bischler–Napieralski reaction. Asymmetric reduction of the resultant dihydroisoquinoline products **10**–**15** with $LiAlH_4$ was also explored to generate 1,2,3,4-tetrahydroisoquinolines **16**–**21** carrying three stereogenic centres.



Scheme 1 The Bischler–Napieralski reaction of 2-phenylethylamides **1** to generate the corresponding 3,4-dihydroisoquinolines **4**. Salts **2** and **3** have been proposed as reaction intermediates (ref. 3).

Results and discussion

The amide substrates **7**–**9** were prepared in a straightforward manner by reaction of either acetyl chloride or benzoyl chloride with amines **5** and **6**[9] as shown in Scheme 2. Treatment of these substrates with $POCl_3$–P_2O_5 in toluene generated the 1,3,4-trisubstituted 3,4-dihydroisoquinolines **10**–**15** as diastereoisomeric mixtures, but with a significant diastereoisomeric bias in each case. The yields of these reactions are poor to moderate (29–60%), a general feature of the Bischler–Napieralski reaction.[1–7]

For the three reactions investigated the diastereoisomeric excesses ranged from 80 to 91% de (Table 1) as determined by ^{1}H-NMR and in the case of **12** and **13** by HPLC analyses of the product mixtures. Substrates **8** and **9**, which gave products **12** (and **13**) and **14** (and **15**), showed the highest diastereoisomeric excesses of 86 and 91% respectively. Recrystallisation of the products gave a crystal of the predominant diastereoisomer in each case, suitable for X-ray structure analysis. The corresponding structures for **12** and **14** are shown in Figs. 1 and 2 respectively. In each case it is clear that the alkyl and aryl

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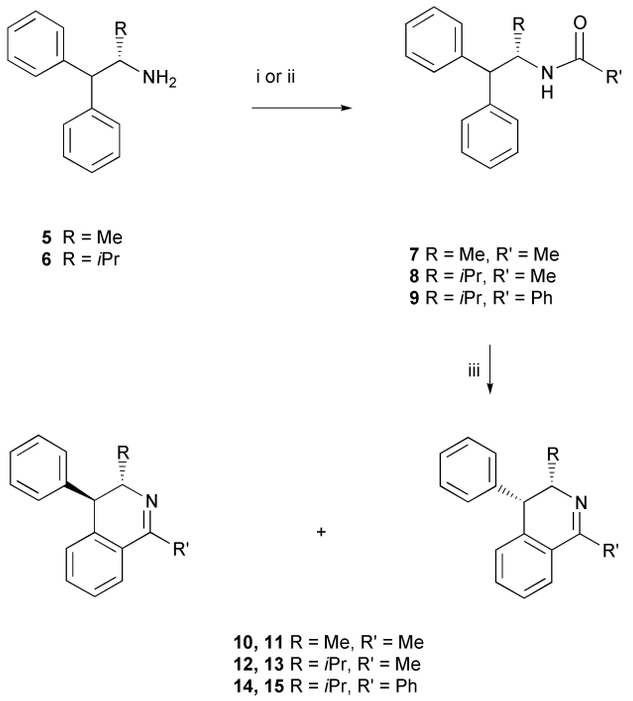
Table 1 Bischler–Napieralski cyclisation products and yields from amides **7**–**9**

Substrate	Product	R	R′	Yield (%)	Diastereoisomer ratios	De[a] (%)	Mp/°C (major isomer)
7	**10**, **11**	Me	Me	29	9 : 1	80	—
8	**12**, **13**	iPr	Me	53	21 : 1	91[a]	65–67 (**12**)
9	**14**, **15**	iPr	Ph	32	13 : 1	86	119–121 (**14**)

[a] Diastereoisomeric excesses were calculated from the ^{1}H-NMR analysis and in the case of **8** by chiral HPLC analysis (Chiralcel OD-H column; hexane–propan-2-ol, 99 : 1; Flow 0.8 ml min^{-1}).



Scheme 2 *Reagents and conditions*: (i) AcCl, Et_3N, CH_2Cl_2, 12 h, 25 °C, 93–94%; (ii) benzoyl chloride, Et_3N, CH_2Cl_2 12 h, 25 °C, 94%; (iii) $POCl_3$, P_2O_5, toluene, 29–60%.

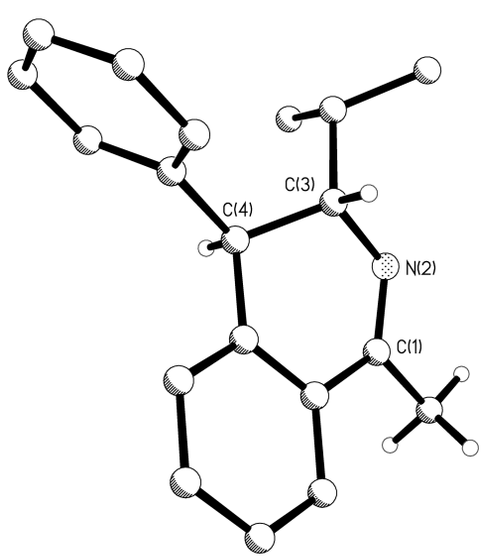


Fig. 1 Ball and stick drawing of the molecular structure of **12** in the solid state showing the relative configuration between the substituents at C(3) and C(4) of the dihydroisoquinoline product after Bischler–Napieralski cyclisation of **8**.

substituents at C(3) and C(4) have a *trans* relative stereochemistry. The absolute stereochemistry is secured with the knowledge that the stereogenic centre at C(3) is derived from the enantiomerically pure (*S*) amides **8** and **9**. In the ^{1}H-NMR spectrum of the crude reaction product **12** (and **13**) derived from **8** the $J_{H3–H4}$ vicinal coupling constant for the major

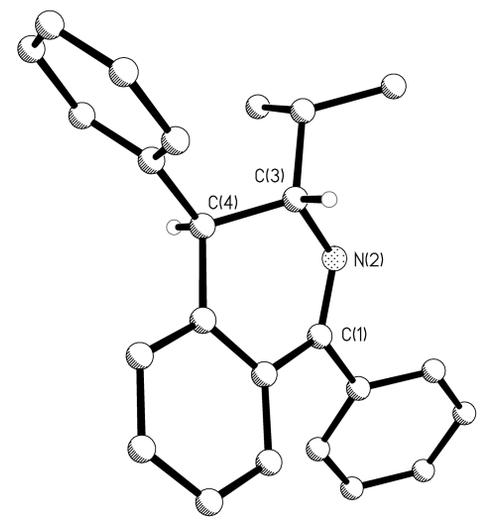


Fig. 2 Ball and stick drawing of the X-ray generated molecular structure of **14** in the solid state showing the relative configuration between the substituents at C(3) and C(4) of the dihydroisoquinoline product after Bischler–Napieralski cyclisation of **9**.

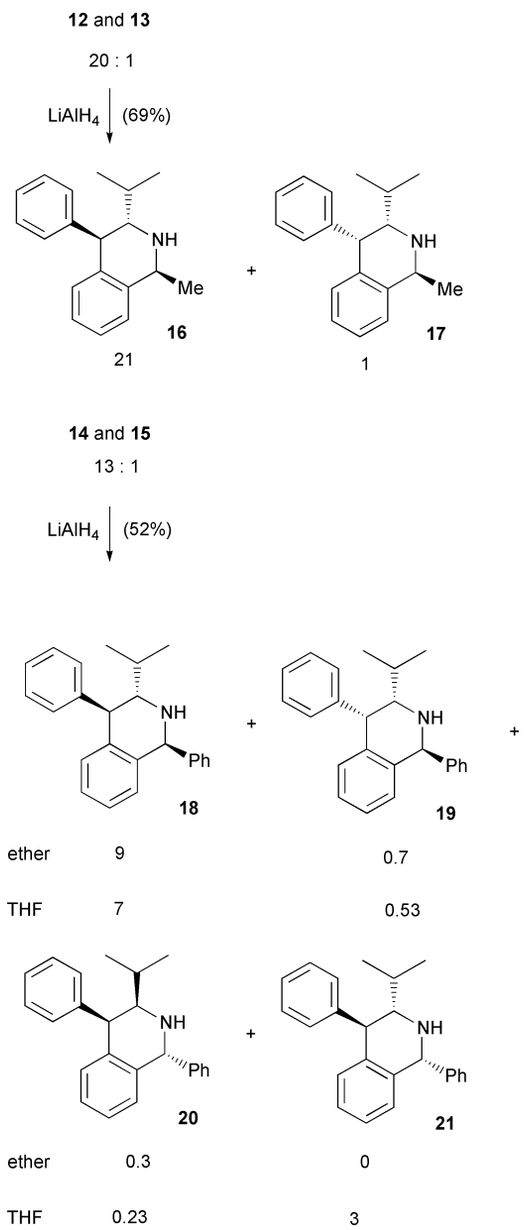
diastereoisomer, **12**, was 9.7 Hz. For the minor diastereoisomer, **13**, this coupling constant was only 5.6 Hz. Similarly the major diastereoisomer **14** of the reaction products derived from amide **9** had the larger $J_{H3–H4}$ vicinal coupling constant (8.7 Hz) and was assigned structure **14**. The minor isomer had the smaller $J_{H3–H4}$ coupling constant (5.3 Hz) consistent with structure **15**. The larger coupling $J_{H3–H4}$ constants for the major diastereoisomers are supported by the *trans* diaxial relationship between the C(3) and C(4) hydrogens as observed in the X-ray structures which were solved for **12** and **14** (Figs. 1 and 2).

With the 3,4-dihydroisoquinolines in hand, albeit as diastereoisomeric mixtures, $LiAlH_4$ reduction of the imine functionality was explored to access the 1,2,3,4-tetrahydroisoquinolines and to assess the stereoselectivity of the reduction. When reduction of **12** (and **13**) (21 : 1) was conducted in ether or THF at reflux a similar ratio of diastereoisomeric products (20 : 1) was observed to that found in the substrate from each experiment. This outcome suggested that the reduction was highly stereospecific and generated products with a *trans* C(1)–C(3) relative stereochemistry. The major diastereoisomer was assigned structure **16**. It retained the larger $J_{H3–H4}$ coupling constant of 7.1 Hz relative to that of 2.4 Hz for the minor diastereoisomeric product. A ^{1}H-NMR difference NOE analysis was carried out and the results were again consistent with structure **16** for the major diastereoisomer. In particular, there was a strong perturbation at H(3) when the C(1) methyl hydrogen signal was irradiated, and *vice versa*. Also there was a strong and reciprocated NOE response between H(1) and H(4) indicating that these hydrogen atoms are on the same face of the ring system.

In the case of compound **14** (and **15**) the stereoselectivity of the $LiAlH_4$ reduction was observably solvent dependent. When the reaction was carried out in ether at reflux the products **18** (and **19**) were formed in a 9 : 1 ratio. Their structures were assigned again by assessing the $J_{H3–H4}$ coupling constants (7.9 Hz for **18** and 3.5 Hz for **19**). It is not clear why this ratio has changed from that found in the starting substrate (13 : 1).

It is possible that with this substrate there has been some isomerisation at C(3) prior to hydride reduction and thus isomer **20**, the mirror image of **19**, emerges as a minor component in the product mixture. This isomer is clearly not resolvable from **19** by ^{1}H-NMR, and therefore the change in bias from 13 : 1 to 9 : 1 may reflect the generation of **20** as a minor component. The predominant products have the alkyl or aryl group at C(1) *trans* to the C(3) isopropyl group in the resultant tetrahydroisoquinolines.

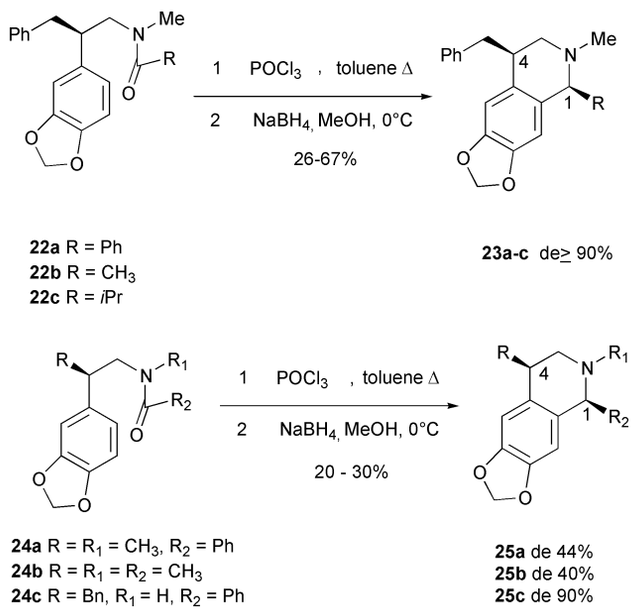
When the reduction was carried out in THF at reflux then a new diastereoisomer was observed by ^{1}H-NMR as a significant product (Scheme 3), in addition to **18** and **19**–**20**. This



Scheme 3

new diastereoisomer was assigned structure **21** on the basis of a $J_{H3–H4}$ coupling constant of 10.3 Hz and ^{1}H-NMR NOE difference analysis and represents hydride delivery to the *Re* face of imine **14**. The stereochemical outcome of these reactions in ether indicates that the $LiAlH_4$ reduction was highly stereoselective and essentially gave exclusive delivery of hydride to the *Re* face of the imine substrates **12** and **14**. We have no definitive hypothesis for this, however it may be assumed that lithium will co-ordinate to the imine nitrogen in an *anti* manner to the C(3) isopropyl group covering the lower (*Si*) face of the imines **10**–**15** (Scheme 2). Aluminium hydride will then be more easily presented to the top (*Re*) face of the imine. Perhaps in THF, lithium is more readily sequestered by the solvent, promoting an increased accessibility of the aluminium hydride to the *Si* face of **14** and thus **21** emerges as a significant product.

In a recent report[5] the cyclisation of enantiomerically pure substrates **22** and **24** followed by *in situ* reduction of the 4-substituted *N*-methyldihydroisoquinolines with $NaBH_4$ resulted in products with diastereoisomeric ratios ranging from 40–90% de as shown in Scheme 4. In that study the major



Scheme 4 Related reductions of Bischler–Napieralski tetrahydroisoquinoline products showing a preference for C(1)–C(4) *cis* products.[5]

products **23** and **25** have the C(1) and C(4) substituents *cis* to each other, similar to those observed in this study. For the reactions illustrated in Scheme 3, reduction of the Bischler–Napieralski generated tetrahydroisoquinolines **12**–**15** was high stereoselective, generating a substantial preference for C(1)–C(4) *cis* products. Additionally the products have a *trans* relationship between the C(1) and C(3) substituents. Clearly the steric interactions arising from the C(3) and C(4) substituents are both reinforcing in the current study and contribute to the extremely high stereoselectivity observed for the reductions in Scheme 3.

In summary, the amides of the amines **5** and **6** have been used to explore an asymmetric Bischler–Napieralski reaction. The cyclisation occurs with good stereoselectivity (80–90% de) to deliver 3,4-dihydroisoquinolines containing two contiguous stereogenic centres at C(3) and C(4). Further reduction of these products with $LiAlH_4$ generates tetrahydroisoquinolines in a completely stereoselective manner, with a *trans* geometry between the substituents at C(1) and C(3) and a preferred *cis* geometry between the substituents at C(1) and C(4), to generate tetrahydroisoquinolines with three stereogenic centres.

Experimental

A GallenKamp GRIFFIN MPA350.BM2.5 melting point apparatus was used to record melting points, which are uncorrected. High-resolution mass spectrometry was performed on a VG AUTOSPEC spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian Gemini 300 MHz spectrometer (^{1}H at 299.98 MHz, ^{13}C at 75.431 MHz). ^{1}H-NMR NOE experiments were conducted on a Varian Unity Plus 500 MHz spectrometer (^{1}H at 500.08 MHz). Chiral HPLC was carried out on a Chiralcel OD-H column with a Varian 9012 HPLC pump and Varian 9012 UV detector. All solvents were dried prior to use and reactions were carried out under an atmosphere of N_2.

Table 2 Selected spectroscopic data for compounds **7**–**20**

Product	IR (ν/cm^{-1})	$[\alpha]_D^{20}/10^{-1}$ deg cm^2 g^{-1}	δ		MS *m*/*z* (rel. int. %)
			^{1}H NMR ($CDCl_3$, 300 MHz)	^{13}C NMR ($CDCl_3$, 75.43 MHz)	
7	(KBr) 3445, 1546 (N–H), 1639 (C=O)	−67.2 (c = 0.64, $CHCl_3$)	1.1 (d, 3H, J = 6.4 Hz, CH–*CH*$_3$), 1.73 (s, 3H, CO–*CH*$_3$), 3.8 (d, 1H, J = 9.8 Hz, Ph$_2$–*CH*), 4.8 (m, 1H, NH–*CH*–CH$_3$), 5.18 (1H, d broad, J = 8.3 Hz, NH D_2O exchangeable), 7.1–7.22 (m, 10H, aromatics)	20.4 (CH_3), 23.4 (CH_3), 47.5 (*C*H–Ph$_2$), 58.1 (*C*H–NH), 126.6, 128.11, 128.2, 128.5, 128.6, 141.8, 142.2 (aromatics), 169.0 (C=O)	(CI-CH_4) 254 (MH^+) (100%), 86 (Me–CH–NH–CO–CH_3) (5%)
8	(KBr) 3407, 1556 (N–H), 1646 (C=O)	−35.3 (c = 0.56, $CHCl_3$)	0.99 (3H, d, J = 6.7 Hz, CH–*CH*$_3$), 1.1 (3H, d, J = 6.7 Hz, CH–*CH*$_3$), 1.8 (3H + 1H, m, CH$_3$–*CH*–CH$_3$ + CO–*CH*$_3$), 4.01 (1H, d, J = 10.6 Hz, Ph$_2$–*CH*), 4.99 (1H, m, NH–*CH*–iPr), 5.18 (1H, d broad, J = 9.1 Hz, NH D_2O exchangeable), 7.2–7.5 (10 H, m, aromatics)	15.5 (CH_3), 21.2 (CH_3), 23.6 (*C*H$_3$–CO), 29.3 (CH$_3$–*C*H–CH$_3$), 55.6 (*C*H–NH), 55.7 (Ph–*C*H–Ph), 126.8, 126.9, 128.2, 128.5, 128.8, 129.2 142.8, 143.0 (aromatics), 170.4 (C=O)	(CI-CH_4) 282 (MH^+) (100%), 114 (*i*Pr–CH–NH–CO–CH_3) (20%)
9	(KBr) 3341, 1532, (N–H), 1635 (C=O)	−29.5 (c = 0.59, $CHCl_3$)	1.0 (3H, d, J = 6.7 Hz, CH–*CH*$_3$), 1.1 (3H, d, J = 6.7 Hz, CH–*CH*$_3$), 1.95 (1H, m, CH$_3$–*CH*–CH$_3$), 4.2 (1H, d, J = 11.1 Hz, Ph$_2$–*CH*), 5.2 (1H, m, NH–*CH*–iPr), 5.8 (1H, d broad, J = 10.1 Hz, NH D_2O exchangeable), 7.1–7.6 (15H, m, aromatics H)	15.5 (CH_3), 20.9 (CH_3), 29.3 (CH$_3$–*C*H–CH$_3$), 55.3 (*C*H–NH), 55.9 (Ph–*C*H–Ph), 126.5, 126.6, 127.8, 128.0, 128.3, 128.6, 130.9 142.3, 142.5 (aromatics), 168 (C=O)	(CI-CH_4) 344 (MH^+) (100%), 176 (Ph–CO$^+$H–NH–CH–*i*Pr) (15%), 75 (*i*Pr–CH–NH) (26%)
10	(NaCl) 1631 (C=N)	—	1.4 (3H, d, J = 6.7 Hz, CH–*CH*$_3$), 2.59 (3H, d, J = 1.9 Hz, N=C–*CH*$_3$), 3.8 (1H, d, J = 11.1 Hz, Ph$_2$–*CH*), 3.9 (1H, m, N–*CH*–CH$_3$), 6.9 (1H, m, aromatic), 7.2–7.5 (7H, m, aromatics H), 7.6 (1H, m, aromatic)	21.8 (CH_3), 23.4 (CH_3), 49.5 (Ph–*C*H–ring), 57.7 (*C*H–N), 126.5, 125.2, 126.8, 127.8, 128.6, 129.0, 140.2, 141.9 (aromatics), 163.3 (C=N)	(CI-CH_4) 236 (MH^+) (100%)
12	(KBr) 1626 (C=N)	—	1.05 (3H, d, J = 6.7 Hz, CH–*CH*$_3$), 1.20 (3H, d, J = 6.7 Hz, CH–*CH*$_3$), 1.85 (1H, m, CH$_3$–*HC*–CH$_3$), 2.6 (3H, d, J = 1.5 Hz, N=C–CH$_3$), 4.0 (1H, dd, J = 8.7, J = 4.8 Hz, N–*CH*–CH–Ph), 4.2 (1H, d, J = 9.7 Hz, N–CH–*CH*–Ph), 6.85 (1H, m, aromatic), 7.15–7.35 (7H, m, aromatics H), 7.58 (1H, m, aromatic)	17.8 (CH_3), 20.9 (CH_3), 23.8 (*C*H$_3$–CN), 30.9 (CH$_3$–*C*H–CH$_3$), 45.3 (Ph–*C*H–ring), 67.8 (*C*H–N), 125.2, 126.9, 127.2, 128.4, 128.9, 129.1, 129.5, 131.0, 140.5, 143.2 (aromatics), 162.9 (C=N)	(EI) 263 (M^+) (44.5%), 248 ($M^+ - CH_3$) (100%), 220 ($M^+ - i$Pr) (220)
14	(KBr) 1608 (C=N)	—	1.06 (3H, d, J = 6.7 Hz, CH–*CH*$_3$), 1.20 (3H, d, J = 6.7 Hz, CH–*CH*$_3$), 1.82 (1H, m, CH$_3$–*HC*–CH$_3$), 3.84 (1H, dd, J = 8.7, J = 4.5 Hz, N–*CH*–CH–Ph), 4.0 (1H, d, J = 8.7 Hz, N–CH–*CH*–Ph), 6.85–7.63 (14H, m, aromatic H)	17.9 (CH_3), 20.5 (CH_3), 21.8 (*C*H$_3$–C=N), 30.2 (CH$_3$–*C*H–CH$_3$), 44.9 (Ph–*C*H–Ph), 67.9 (*C*H–N), 124.2–129.0, 141.2, 142.3 (aromatics), 165.4 (C=N)	(CI-CH_4) 326 (MH^+) (100%)
16	—	—	0.98 (3H, d, J = 7.1 Hz, CH–*CH*$_3$), 1.01 (3H, d, J = 7.1 Hz, CH–*CH*$_3$), 1.56 (3H, d, J = 6.6 Hz, NH–CH–*CH*$_3$), 1.7 (1H, m, CH$_3$–*HC*–CH$_3$), 2.97 (1H dd, J = 6.2, J = 6.2 Hz, NH–*CH*–CH–Ph), 4.0 (1H, d, J = 7.1 Hz, NH–CH–*CH*–Ph), 4.3 (1H, q, J = 6.6 Hz, *CH*–CH$_3$), 6.80–7.3 (9H m aromatics)	16.7 (CH_3), 20.8 (CH_3), 23.5 (*C*H$_3$–CH–NH), 27.7 (CH$_3$–CH–CH$_3$), 47.9 (NH–CH–*C*H–Ph), 49.4 (–ring–*C*H–Me), 61.1 (NH–*C*H–CH–Ph), 128.2–130.4, 137.3, 140.7, 145.2 (aromatics)	(CI-CH_4) 266 (MH^+) (100%); 222 (MH^+ − NH–CH–CH$_3$) (22%)
18	—	—	0.8 (3H, d, J = 6.8 Hz, CH–*CH*$_3$), 1.01 (3H, d, J = 6.8 Hz, CH–*CH*$_3$), 1.67 (1H, m, CH$_3$–*HC*–CH$_3$), 2.84 (1H, dd, J = 7.9, J = 4.9 Hz, NH–*CH*–CH–Ph), 4.1 (1H, d, J = 7.9 Hz, NH–CH–*CH*–Ph), 5.3 (1H, s, *CH*–Ph), 6.90–7.45 (14 H, m, aromatic)	16.3 (CH_3), 20.6 (CH_3), 27.7 (CH$_3$–*C*H–CH$_3$), 47.9 (NH–CH–*C*H–Ph), 58.9 (NH–*C*H–ring), 61.1 (NH–*C*H–CH–Ph), 128.2–130.4, 137.1, 139.2, 144.9, 145.2, 140.7, 145.2 (aromatics)	(CI-CH_4) 328 (MH^+) (100%)

(*S*)-*N*-(1-Methyl-2,2-diphenylethyl)acetamide 7

Triethylamine (0.34 ml, 2.41 mmol) and acetyl chloride (0.13 ml, 1.77 mmol) were added dropwise to a solution of amine **5** (340 mg, 1.61 mmol) in DCM (15 ml) at 0 °C. The reaction was stirred at 25 °C for 12 h and was then worked up by washing with water (3 × 20 ml). The organic layer was dried ($MgSO_4$), filtered and evaporated under reduced pressure and the residue was purified by recrystallisation (petrol–acetone 90 : 10) to give the product amide **7** as a colourless crystalline salt (389 mg, 94%). Mp 104–106 °C. For spectroscopic data see Table 2 (Found MH^+, 254.1545. $C_{17}H_{19}NO$ requires MH 254.1551).

(*S*)-*N*-(1-Benzhydryl-2-methylpropyl)acetamide 8

Triethylamine (0.88 ml, 6.27 mmol) and acetyl chloride (0.33 ml, 4.60 mmol) were added dropwise to a solution of amine **7** (1 g, 4.18 mmol) in DCM (40 ml) 0 °C and the mixture was then heated under reflux for 4 h. The reaction was washed with water (3 × 30 ml) and the organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to leave an amorphous powder. This material was recrystallised from hexane–ethyl acetate (85 : 15) to obtain the title amide **8** as a colourless crystalline solid (1.10 g, 94%). Mp 130–132 °C. For spectroscopic data see Table 2 (Found MH^+, 282.1858. $C_{19}H_{23}NO$ requires MH 282.1850).

(*S*)-*N*-(1-Benzhydryl-2-methylpropyl)benzamide 9

Triethylamine (0.40 ml, 2.19 mmol) and acetyl chloride (0.26 ml, 1.61 mmol) were added to a solution of amine **6** (350 mg, 1.46 mmol) in DCM (20 ml) at 0 °C and the reaction was stirred for 12 h at 25 °C. The reaction mixture was washed with water (3 × 20 ml) and the organic layer was dried ($MgSO_4$), filtered and evaporated under reduced pressure. The product was recrystallised from ethanol–water (80 : 20) to obtain the title amide **9** as a colourless crystalline solid (410 mg, 94%). Mp 221–223 °C (Found MH^+, 344.2009. $C_{24}H_{26}N_1O$ requires MH, 344.2014). For spectroscopic data see Table 2.

(3*S*,4*S*)-1,3-Dimethyl-4-phenyl-3,4-dihydroisoquinoline 10 and (3*S*,4*R*)-1,3-dimethyl-4-phenyl-3,4-dihydroisoquinoline 11

Phosphoryl chloride (1.35 g, 9.4 mmol) was added dropwise to a suspension of phosphorus pentoxide (0.86 ml, 9.4 mmol) in a solution of amide **7** (200 mg, 0.94 mmol) in anhydrous toluene (25 ml). After complete addition the reaction mixture was heated under reflux for 12 hours and then crushed ice (25 g) was added. The organic layer was separated and the aqueous residue was made basic with sodium hydroxide (15% w/v) solution and the product extracted into chloroform (3 × 25ml). The chloroform extract was dried ($MgSO_4$), evaporated under reduced pressure and the product purified over silica (50 : 50 hexane–ethyl acetate) to give **10**–**11** as a yellow oil (47 mg, 29%) (Found MH^+, 236.1444. $C_{17}H_{18}N_1$ requires MH, 236.1431). For spectroscopic data see Table 2.

(3*S*,4*S*)-1-Methyl-3-isopropyl-4-phenyl-3,4-dihydroisoquinoline 12 and (3*S*,4*R*)-1-methyl-3-isopropyl-4-phenyl-3,4-dihydroisoquinoline 13

Phosphoryl chloride (3.25 ml, 35 mmol) was added dropwise to a suspension of phosphorus pentoxide (5.0 g, 35 mmol) in a solution of amide **8** (1.0 g, 3.54 mmol) in anhydrous toluene (60 ml). After complete addition the reaction mixture was heated under reflux for 12 hours and then crushed ice (60 g) was added. The organic layer was separated, the aqueous residue was made basic with sodium hydroxide (15% w/v) solution and the product was then extracted into chloroform (3 × 25ml). The chloroform extract was dried ($MgSO_4$), evaporated under reduced pressure and the product purified over silica (95 : 5 petrol–acetone) to give **12**–**13** as a colourless amorphous solid (558 mg, 60%) (Found M^+, 263.1666. $C_{19}H_{21}N_1$ requires M, 263.1674). For spectroscopic data see Table 2.

(3*S*,4*S*)-3-Isopropyl-1,4-diphenyl-3,4-dihydroisoquinoline 14 and (3*S*,4*R*)-3-isopropyl-1,4-diphenyl-3,4-dihydroisoquinoline 15

Phosphoryl chloride (1.24 g, 8.9 mmol) was added dropwise to a suspension of phosphorus pentoxide (0.80 ml, 8.9 mmol) in a solution of amide **9** (303 mg, 0.88 mmol) in anhydrous toluene (25 ml). After complete addition the reaction mixture was heated under reflux for 12 hours and was then quenched by the addition of crushed ice (25 ml). The aqueous residue was made basic by the addition of sodium hydroxide (15% w/v) solution and the product was then extracted into chloroform (3 × 25ml). The chloroform extract was dried ($MgSO_4$), evaporated under reduced pressure and the product purified over silica (90 : 10 hexane–ethyl acetate) to give **14**–**15** as a colourless crystalline solid (91 mg, 32%) (Found MH^+, 326.1915. $C_{24}H_{23}N$ requires MH, 326.1908). For spectroscopic data see Table 2.

(1*S*,3*S*,4*S*)-1-Methyl-3-isopropyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline 16 and (1*S*,3*S*,4*R*)-1-methyl-3-isopropyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline 17

A solution of **14**–**15** (352 mg, 1.33 mmol) in ether (30 ml) was added dropwise at 0 °C to a suspension of $LiAlH_4$ (504 mg, 13.3 mmol) in ether (10 ml) and the reaction was heated under refluxed for 24 h. The reaction was then quenched with 5% HCl, the aqueous layer made basic with 15% NaOH and the products extracted into ether (3 × 30 ml). The organic extract was dried ($MgSO_4$) and evaporated under reduced pressure to give **16** and **17** as a colourless oil (242 mg, 69 %) (Found MH^+, 266.1901. $C_{19}H_{24}N$ requires MH, 266.1908). For spectroscopic data see Table 2.

(1*S*,3*S*,4*S*)-3-Isopropyl-1,4-diphenyl-1,2,3,4-tetrahydroisoquinoline 18, (1*S*,3*S*,4*R*)-3-isopropyl-1,4-diphenyl-1,2,3,4-tetrahydroisoquinoline 19 and (1*R*,3*R*,4*S*)-3-isopropyl-1,4-diphenyl-1,2,3,4-tetrahydroisoquinoline 20

A solution of **16**–**17** (48 mg, 0.147 mmol) in ether (5 ml) was added dropwise at 0 °C to a suspension of $LiAlH_4$ (56 mg, 1.47 mmol) in ether (5 ml). The reaction was heated under reflux for 24 h and was then quenched with 5% HCl. The aqueous layer was made basic with 15% NaOH and the products were extracted into ether (3 × 10 ml). The organic extract was dried ($MgSO_4$) and evaporated under reduced pressure to give **18** (and **19**–**20**) as a colourless oil (25 mg, 52%) (Found MH^+, 328.2058. $C_{24}H_{26}N$ requires MH, 328.2065). For spectroscopic data see Table 2.

Crystal structure determination of 12 and 14†

Data for both compounds were measured on a Bruker SMART diffractometer with graphite monochromated Mo-Kα radiation (λ = 0.7107 Å) using 0.3° width steps accumulating area detector frames spanning a hemisphere of reciprocal space for both structures; the reflections were corrected for Lorentz and polarisation effects. Absorption effects were corrected on the basis of multiple equivalent reflections.

The structures were solved by direct methods and refined by full matrix least squares on F^2 using the program SHELXTL. All hydrogen atoms were included in calculated positions using a riding model. All non-hydrogen atoms were refined as anisotropic.

† CCDC reference numbers 168569 and 168570. See http://www.rsc.org/suppdata/p1/b1/b106942j/ for crystallographic files in .cif or other electronic format.

Crystal data for 12. $C_{19}H_{21}N$, M = 263.37, orthorhombic, space group $P2_12_12_1$, a = 5.9721(3), b = 8.5759(4), c = 30.5762(9) Å, V = 1565.99(12) Å^3, T = 293(2) K, Z = 4, μ-(Mo-Kα) = 0.064 mm^{-1}, colourless block, crystal dimensions 0.1 × 0.1 × 0.07 mm. Full matrix least squares based on F^2 gave $R1$ = 0.0344 for 1739 ($F > 4\sigma(F)$) and $wR2$ = 0.0678 for all data, GOF = 0.872 for 182 parameters.

Crystal data for 14. $C_{24}H_{23}N$, M = 325.43, orthorhombic, space group $P2_12_12_1$, a = 9.4794(3), b = 10.2277(3), c = 19.5795(4) Å, V = 1898.28(9) Å^3, T = 293(2) K, Z = 4, μ-(Mo-Kα) = 0.065 mm^{-1}, colourless block, crystal dimensions 0.1 × 0.1 × 0.07 mm. Full matrix least squares based on F^2 gave $R1$ = 0.0460 for 2014 ($F > 4\sigma(F)$) and $wR2$ = 0.0869 for all data, GOF = 0.957 for 227 parameters.

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