Atroposelectivity in the reactions of ortholithiated aromatic tertiary amides with aldehydes

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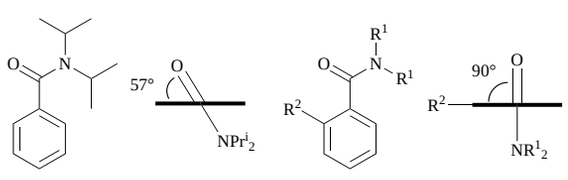
The products of the addition of ortholithiated *N*,*N*-dialkylnaphthamides to aldehydes are pairs of stable, diastereoisomeric atropisomers, formed with selectivities of up to 90 : 10 in favour of the *syn*-atropisomer.

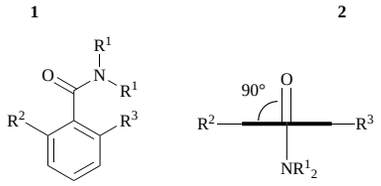
Introduction

Directed metallation is a regioselective reaction, and electrophilic capture of lithiated aromatic amides and carbamates is a powerful method for regioselective synthesis of *ortho*-disubstituted aromatic rings.[1,2] Although this reaction has made its home in the flat world of aromatic chemistry, it has on occasions also been shown to have stereoselective attributes. An early example was Mukaiyama's chiral-auxiliary-controlled addition of a lithiated aminal to aldehydes.[3] Lithiated chiral oxazolines[4] and amides[5] have been added to aldehydes, but with only poor levels of stereocontrol. More recently the use of arene–chromium tricarbonyl complexes has allowed ortholithiation reactions to be made enantioselective by the use of chiral bases,[6–12] or acetal[13,14] or aminal[15,16] chiral auxiliaries.

Aromatic chemistry is rarely truly flat, and indeed one of the most powerful directors of aromatic ortholithiation, the tertiary amide group,[2] cannot lie in the plane of the aromatic ring for steric reasons. In *N*,*N*-diisopropylbenzamide **1**, steric hindrance surrenders to conjugation when the amide is twisted at an angle 57° to the ring,[17] but in 2-substituted[17] or 2,6-disubstituted‡ *N*,*N*-dialkylbenzamides **2** or **3** steric hindrance totally dominates the ground state conformation and the amide and ring lie more or less perpendicular.

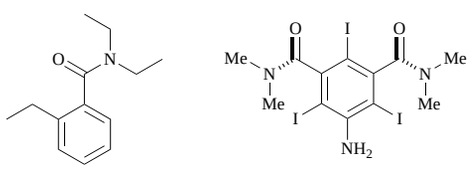


1 **2**

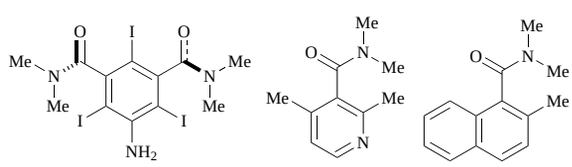


3

For unsymmetrically substituted tertiary amides such as **2** or **3** ($R^2 \neq R^3$), the chirality which results from this perpendicular arrangement manifests itself spectroscopically in the diastereotopicity of CH_2 or $CHMe_2$ groups attached to the amide[5,19–22] or the ring.[23] The coalescence of the proton NMR signals of these diastereotopic groups at high temperatures §[,24–26] has shown the chirality of 2-substituted benzamides **2** to be transient, with the barrier to interconversion of the enantiomers of **4** in DMSO being 60 kJ mol^{-1},[25] corresponding to a half-life for racemisation of 0.004 at 20 °C. In 2,6-disubstituted benzamides **3**, however, steric hindrance slows rotation about the C–CO bond to the point where atropisomers (that is, conformers that are stable on the laboratory timescale[28]) can be isolated. The first successful example was the separation of **5** into a *meso* and a racemic diastereomer and the resolution of



4 *meso*-**5**



(±)-**5** **6** **7**

the latter into two atropisomeric enantiomers.[29,30] The work of Ohno and co-workers[31,32] and of Buck and co-workers[33–36] has highlighted the role of hindrance to amide planarity in the mechanism of action of NADH, and the simple nicotinamide **6** has been resolved into two atropisomeric enantiomers.[33] Amides **7** have been resolved by chromatography on chiral stationary phases by Mannschreck and co-workers[37,38] and by Pirkle *et al.*[39]

Along with NMR experiments,[40–42] these resolutions have allowed the barriers to racemisation of 2,6-disubstituted *N*,*N*-dialkylbenzamides **3** to be determined, and many are enantiomerically stable for several hours in solution at room temperature. Chromatographic separation of diastereoisomeric 2,6-disubstituted benzamides has been reported by Bates *et al.*[43] and by Hudlický *et al.*[44]

Provided it suffers sufficient steric hindrance to rotation, then, an aromatic carboxamide group may confer axial chirality on a molecule. More specifically, the synthesis of a 2,6-disubstituted benzamide **3** from a 2-substituted benzamide **2** creates a new element of chirality. Thayumanavan *et al.*[45] have shown that this process can be made enantioselective by treating *N*,*N*-dialkylnaphthamides **8** with Bu^{s}Li–sparteine to make enentiomerically enriched atropisomeric 2-methylnaphthamides **9** (Scheme 1). In this paper, we describe experiments in the

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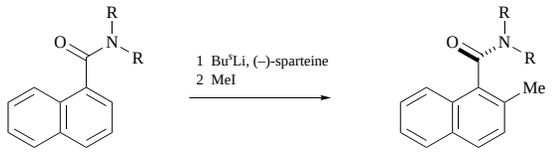
‡ Molecular modelling or X-ray crystallography of a number of *N*,*N*-dialkylnaphthamides has given values within 5° of perpendicular for the dihedral angle between the aromatic ring and the plane of the amide group.[18]

§ Measurement of the barrier to rotation about the partial double bond in *N*,*N*-dialkylamides was a classic application of VT NMR spectroscopy.[24,27]



8 **9** 30% yield, 50% ee

Scheme 1

racemic series which demonstrate that the addition of lithiated *N*,*N*-dialkylnaphthamides to aldehydes, a reaction in which two new chiral elements (a chiral centre and a rotationally restricted C–CO bond) are generated, is diastereoselective.[46]

Results and discussion

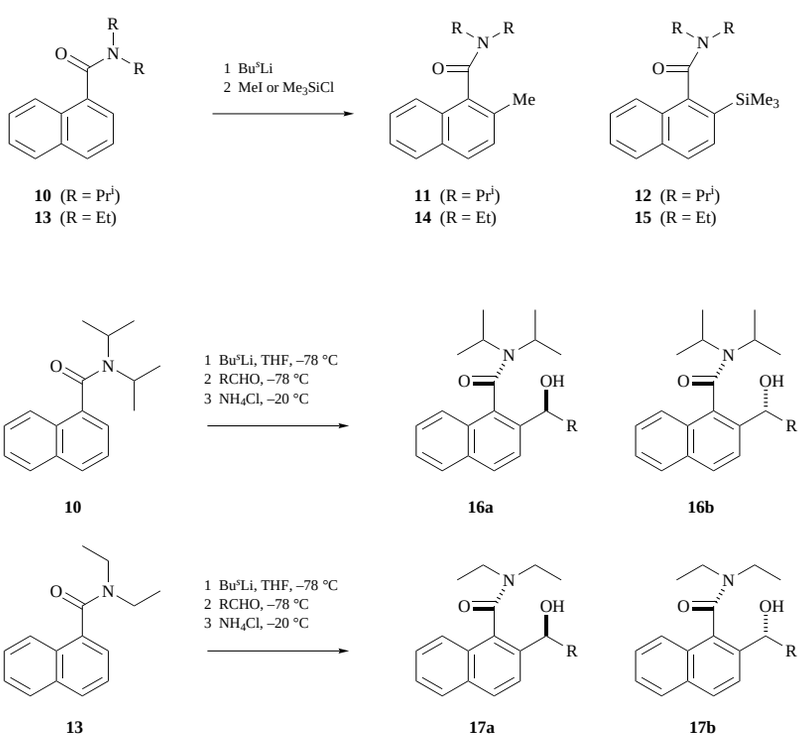
The proton NMR spectrum of *N*,*N*-diisopropyl-1-naphthamide **10** at 20 °C shows four clear diastereotopic methyl doublets, and we determined that the barrier to racemisation of this compound was 75 kJ mol^{-1} by variable temperature NMR spectroscopy in DMSO solution. The barrier to racemisation of *N*,*N*-diethyl-1-naphthamide **13** was somewhat lower at 65 kJ mol^{-1},¶ and although one of the CH_2 groups is split into a diastereotopic pair of signals, these signals are broad in the proton NMR spectrum at 20 °C. Both of these compounds were ortholithiated [Bu^{s}Li, THF, −78 °C (we found that the addition of TMEDA[1] was unnecessary)] and gave 2-substituted naphthamides **11**, **12**, **14** and **15** with methyl iodide or trimethylsilyl chloride. The ^{1}H NMR spectra of **11** and **14** indicated that the molecules were still chiral on the NMR timescale even at 150 °C and 170 °C respectively in 1,2-dichlorobenzene. The chirality of all four 2-substituted compounds was demonstrated by resolving them into two enantiomers by analytical HPLC on a chiral stationary phase (Whelk-O1).[39]

There are several reports of the addition of ortholithiated naphthamides to aldehydes.[47–54] In none of these cases was an alcohol isolated — heating with acid converted it directly into the required lactone, so any stereoselectivity the reaction may have possessed passed unnoticed. We wanted to investigate the stereochemistry of the addition, so we took our two naphthamides **10** and **13**, ortholithiated them under the same conditions and added aldehydes to them at −78 °C. The reactions were warmed to −20 °C and then quenched with ammonium chloride (Scheme 2). A small aliquot was extracted and kept cold for analytical HPLC, the remainder being worked up rapidly and the crude product mixture kept cool to prevent thermal epimerisation. The product ratio was determined by analytical HPLC of the extracted aliquot and the identity of the HPLC peaks confirmed by flash column chromatography of the product mixture and separate characterisation of the two atropisomers **16a** and **16b** or **17a** and **17b** after preparative HPLC. The purified atropisomers were stable compounds and interconverted only slowly in dichloromethane solution at room temperature (the ratio of atropisomers after work-up was little changed from the aliquots extracted at 0 °C, and the composition of solutions kept at −18 °C for 4 to 9 weeks remained constant).

The yields and diastereoisomeric ratios obtained in these reactions are shown in Table 1. In every case, the more retained (more polar) diastereoisomer **16a** or **17a** predominated and we take this consistent polarity difference, along with the consistent differences in the NMR spectra of the two atropisomers detailed below, as evidence that the reaction proceeds with the same sense of diastereoselectivity (which we term atroposelectivity[55]) in every case. The *minor* diastereoisomer was identified in one case (**16b**, R = Ph) by determination of an X-ray crystal structure (Fig. 1), and from this we deduce that the reaction consistently produces predominantly the *syn*-isomer, and assign *syn*-stereochemistry to **16a** and **17a** and *anti*-stereochemistry to **16b** and **17b**. The degree of selectivity is greater for the diisopropyl amides **16** than the diethyl amides **17**, and best selectivities were found with propionaldehyde (R = Et). Selectivity dropped when R was smaller or larger than ethyl. The observed selectivities must arise by kinetic control—the products eventually equilibrate to a thermodynamic ratio of approximately 1:1 on standing for long periods of time in solution at room temperature.

The X-ray crystal structure of **16b** (R = Ph) shown in Fig. 1 illustrates the perpendicular relationship between the amide

¶ The barrier to racemisation of this compound in $CHCl_3$ at 5 MPa pressure has been reported[25] as 63 kJ mol^{-1}.



10 (R = Pr^i) **13** (R = Et) **11** (R = Pr^i) **14** (R = Et) **12** (R = Pr^i) **15** (R = Et)

10 **16a** **16b**

13 **17a** **17b**

Scheme 2

Table 1 Atropisomers obtained from addition of lithiated amides to aldehydes

R	Yield **16** (%)	Ratio **16a**:**16b**	Yield **17** (%)	Ratio **17a**:**17b**
Me	92	85:15	67	77:23
Et	79	90:10	76	78:22
n-C_5H_{11}	75	82:18	85	77:23
Pr^i	91	77:23	85	70:30
Ph	89	72:28	85	51:49

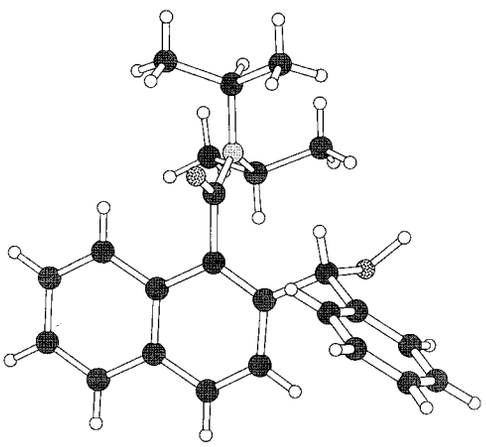


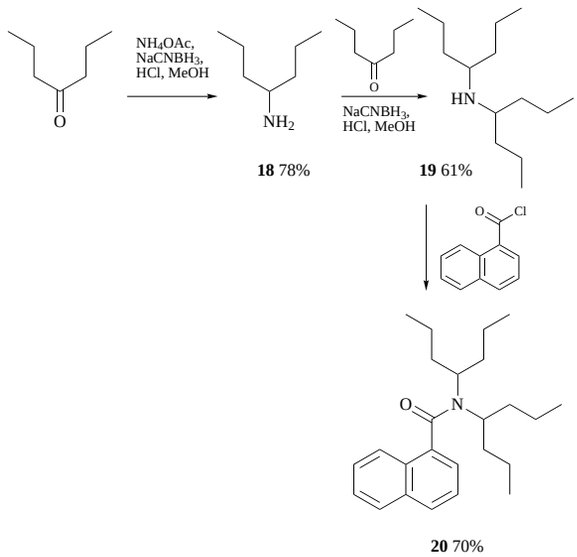
Fig.1 X-Ray crystal structure of **16b** (R = Ph)

group and the naphthalene ring. The dihedral angle between the C=O and C(1)–C(2) bonds is, in this case, 89.3°.‖

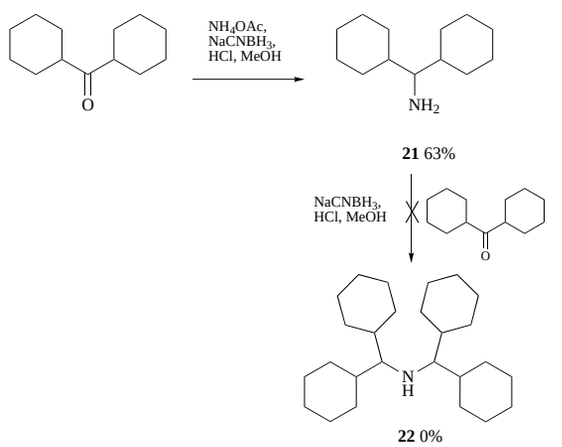
In an attempt to increase the stereoselectivity of these reactions, we made the more bulky bis(1-propylbutyl) amide **20**. Two sequential reductive aminations using heptan-4-one gave **18** then **19**, which was converted straightforwardly to the amide **20** by reaction with 1-naphthoyl chloride (Scheme 3). An attempt to make an even more bulky amine **22** from dicyclohexyl ketone (Scheme 4) failed at the second amination, presumably because of the extreme steric hindrance of primary amine **21**.

Surprisingly, attempted lithiation of the bis(1-propylbutyl) amide **20** with Bu^sLi (in the presence or absence of TMEDA) resulted largely in addition of the organolithium to the naphthyl ring to give **23** as a mixture of diastereoisomers,** and only a moderate yield of aldehyde **24** was obtained when the reaction was quenched with DMF (Scheme 5). Lithiation with Bu^tLi was more successful, but the ortholithiated amide reacted with aldehydes to give the alcohols **25** in poor yield and with low atroposelectivity: with acetaldehyde the two atropisomers **25a** and **25b** (R = Me) were isolated in 14 and 21% yield; with benzaldehyde the atropisomers **25a** and **25b** (R = Ph) were isolated in 11 and 25% yield. The size of the NR_2 group now appears too great: the alkyllithium is diverted from the edge-on approach required for ortholithiation towards the face-on approach leading to addition to the ring, and the aryllithium which does form is too hindered to react satisfactorily with aldehydes.

In contrast with the *formation* of aryllithiums by directed lithiation,[2,56] relatively little is known about the detailed mechanism of the *reaction* of aryllithiums with electrophiles. Aryllithiums generally exist as monomer–dimer mixtures in THF,



Scheme 3



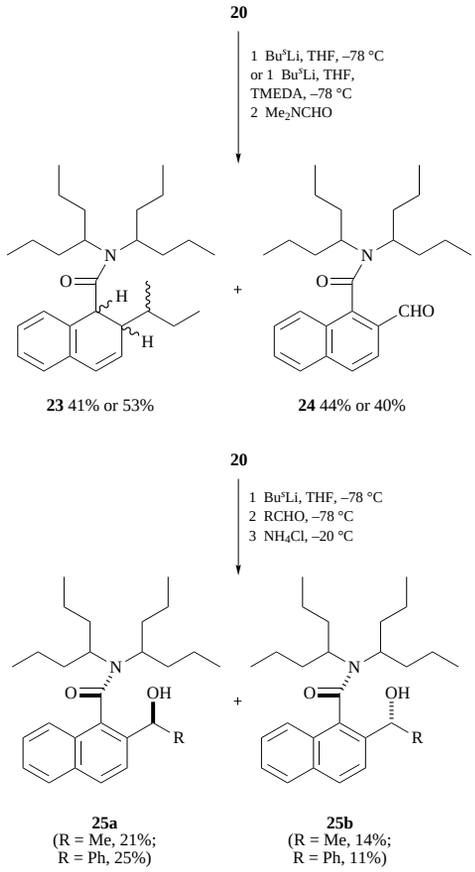
Scheme 4

though it seems likely that at this concentration they react as monomers.[57–60] The most likely geometry for a transition state is the one shown in Scheme 6, in which lithium is smoothly transferred from C to O, the lithium-bearing carbon assumes a temporary tetrahedral shape, and the excess of electrons in the transition state can be dissipated into the aromatic ring system. The stereochemical sense of our reactions suggests attack of the aldehyde on the more hindered face of the aryllithium, with the R group held clear of the amide nitrogen's substituents. The requirement of the lithium for tetrahedral coordination may well be the mediator of this selectivity, with displacement of a ligand from this lithium coordination site either being thermodynamically favoured (the aldehyde carbonyl group is smaller than THF in this hindered position) or generating a more reactive aryllithium–aldehyde complex. Introducing a chelating ligand in an attempt to disrupt this transition state had no effect: lithiated *N*,*N*-diisopropylnaphthamide **10** reacted with propionaldehyde with an almost unchanged 88:12 selectivity in the presence of TMEDA.

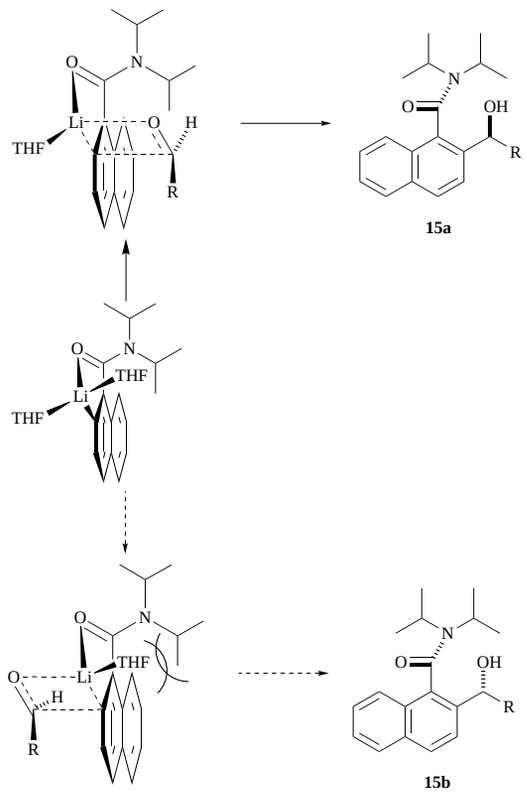
Whatever the origin of the selectivity in all these reactions, we have demonstrated for the first time that the stereochemical course of the reactions of lithiated tertiary amides, widely used in directed metallation chemistry, is controlled by the conformation of the $CONR_2$ amide group. Up to 90% of a single atropisomer may be formed in the reactions of these compounds with aldehydes. These are few examples of diastereoselective syntheses of atropisomers apart from the biaryls,[61] though the atropisomeric chirality of another class of conformationally restricted amides has been used to control the formation of new chiral centres highly effectively.[55,62]

‖ Atomic coordinates, thermal parameters and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1997, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 207/127.

** Ortholithiation must require the alkyllithium to approach the 2-proton more or less in the plane of the aromatic ring. Addition to the ring on the other hand means the alkyllithium can steer well clear of the bulky NR_2 groups, approaching the ring at an angle and *syn* to oxygen. Thayumanavan *et al*. have observed competing addition of Bu^sLi to *N*,*N*-dialkylnaphthamides.[45]



Scheme 5



Scheme 6

Identification of the atropisomers

We are confident that the sense of the diastereoselectivity in these reactions is the same in every case (a) because the major compound is always the more polar and (b) because of consistent differences between the NMR spectra of the more polar and less polar atropisomers. The most significant of these differences are: (i) in the ^{13}C chemical shift of the C=O carbon, which is consistently about 1 ppm further downfield in the major diastereoisomer **16a** or **17a** than in the minor diastereoisomer **16b** or **17b**, and (ii) in the ^{13}C chemical shift of the CHOH carbon, which is consistently about 1 ppm further upfield in the major diastereoisomer than in the minor diastereoisomer. We therefore reason that the *anti*-stereochemistry shown by the X-ray crystal structure of **16b** (R = Ph) (Fig. 1) is a reliable guide to the relative stereochemistry of all of these products. Stereochemical assignment of **25a** and **25b** is provisional and based purely on their elution order.

Experimental

Flash chromatography refers to chromatography carried out on silica by the method of Still *et al.*[63] Analytical HPLC was carried out on a Waters Z Module (10 cm by 8 mm, packed SiO_2 stationary phase) at room temperature using a Waters 510 pump with the flow rate at 2.0 ml min^{-1}. Detection was at 280 nm using a Perkin-Elmer LC 480 Auto Scan Diode Array detector. Preparative HPLC was carried out on a Dynamax-60A column at room temperature using a Gilson 305 Pump with flow rate at 15.0 ml min^{-1}. Detection was at 280 nm using a Gilson 115 UV Detector. Retention times (t_r) were measured by analytical HPLC using the stated solvent system. Ether refers to diethyl ether. *J* Values are given in Hz.

General procedure for synthesis of amides[49]

Thionyl chloride (1.83 ml, 0.025 mol) was added to a solution of 1-naphthoic acid (4.000 g, 0.023 mol) in dichloromethane (5 ml) and the mixture stirred under a drying tube for 2.5 h and evaporated under reduced pressure to give the crude acyl chloride as a dark brown oil. Ether (10 ml) and a solution of the dialkylamine (0.05 mol) in ether (10 ml) was added at 0 °C over a period of 45 min. Stirring was continued for 2 h at room temperature. The mixture was diluted with ether and washed with water and the aqueous phase extracted with ether (50 ml × 2). The organic phases were combined and washed with 1 M hydrochloric acid (50 ml × 2), water (50 ml × 2) and brine (100 ml), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude amide.

N,*N*-Diisopropyl-1-naphthamide 10

In this way, 1-naphthoic acid (4.000 g, 0.023 mol) and diisopropylamine (6.90 ml, 0.049 mol) gave a crude pale brown solid, which was recrystallised from ethyl acetate to give pale brown needles (2.791 g, 47%), mp 183–184 °C (lit.,[64] 181–182 °C); ν_{max}(film)/cm^{-1} 1622 (C=O); δ_H(200 MHz; $CDCl_3$) 8.0–7.3 (7 H, m, ArH), 3.63 (2 H, m, NCH × 2), 1.75 (3 H, d, *J* 7), 1.68 (3 H, d, *J* 7),1.15 (3 H, d, *J* 7) and 1.06 (3 H, d, *J* 7) (CH_3 × 4); δ_C(75 MHz; $CDCl_3$) 170.1 (C=O), 136.9, 133.6, 129.6, 128.3, 128.2, 126.7, 126.3, 125.3, 125.0, 122.1 (Ar), 51.1, 46.0 (NCH × 2), 20.9, 20.8, 20.75 and 20.7 (CH_3 × 4); *m*/*z* (EI) 255 (63%, M^+).

N,*N*-Diethyl-1-naphthamide 13

In the same way, 1-naphthoic acid (4.000 g, 0.023 mol) and diethylamine (5.09 ml, 0.049 mol) gave a crude brown oil, which was distilled, bp 158–160 °C/0.4 mmHg (lit.,[65] 145–148 °C/0.3 mmHg) to give the amide **13** as an oil (2.98 g, 57%); ν_{max}(film)/cm^{-1} 1630 (C=O); δ_H(200 MHz; $CDCl_3$; 298 K) 7.9–7.2 (7 H, m, ArH), 3.85 (1 H, br m, CH_AH$_B$), 3.55 (1 H, br m, CH$_A$$H_B$), 3.1 (2 H, q, *J* 8, CH_2), 1.38 (3 H, t, *J* 7, CH_3) and 1.00 (3 H, t, *J* 7, CH_3); δ_C(75 MHz; $CDCl_3$) 170.3 (C=O), 135.2, 133.5, 129.6, 128.8, 128.4, 126.9, 126.4, 125.2, 124.8, 123.2 (Ar), 43.1, 39.1 (CH_2 × 2), 14.3 and 13.1 (CH_3 × 2); *m*/*z* (EI) 227 (92%, M^+); δ_H(200 MHz; $CDCl_3$; 203 K) 7.9–7.4 (7 H, m, ArH), 3.90 (1 H, dq, *J* 14, 7, CH_AH$_B$), 3.45 (1 H, dq, *J* 14, 7, CH$_A$$H_B$), 3.08 (2 H, m, CH_2), 1.35 (3 H, t, *J* 7, CH_3) and 0.96 (3 H, t, *J* 7, CH_3).

_N,N_-Diisopropyl-2-methyl-1-naphthamide 11

sec-Butyllithium (1.8 ml of a 1.3 M solution in cyclohexane, 2.4 mmol) was added to a stirred solution of *N*,*N*-diisopropyl-1-naphthamide **10** (0.561 g, 2.2 mmol) in dry THF (40 ml) under nitrogen at −78 °C. After 30 min, methyl iodide (0.27 ml, 4.4 mol) was added to the yellow–sepia solution. The mixture was stirred for a further 30 min at −78 °C then allowed to warm to 0 °C. Saturated aqueous ammonium chloride and water were added and the mixture was extracted with CH_2Cl_2 (10 ml × 3). The combined organic fractions were washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure to give a crude product which was recrystallised from ethyl acetate to give the *amide* **11** as needles (0.283 g, 48%), mp 192–192.5 °C; ν_{max}(film)/cm^{-1} 2968, 1617, 1441 and 1321; δ_H(300 MHz; $CDCl_3$) 7.9–7.2 (6 H, m, Ar), 3.58 (2 H, septet, *J* 7, NCH × 2), 2.47 (3 H, s, ArCH_3), 1.76 (3 H, d, *J* 7), 1.65 (3 H, d, *J* 7), 1.09 (3 H, d, *J* 7) and 0.98 (3 H, d, *J* 7) [(CH_3)$_2$CH × 4]; δ_C(75 MHz; $CDCl_3$) 169.8 (C=O), 134.6, 131.6, 130.7, 129.8, 128.5, 128.0, 127.7, 126.5, 125.4, 124.6 (Ar), 51.1, 46.1 (NCH × 2), 21.2, 21.1, 20.8, 20.7 (CHMe_2 × 2) and 19.3 (ArCH_3) (Found: C, 80.3; H, 8.54; N, 5.10%; M$^+$, 269.1783. $C_{18}H_{23}NO$ requires C, 80.2; H, 8.61; N, 5.20%; *M*, 269.1780).

_N,N_-Diisopropyl-2-trimethylsilyl-1-naphthamide 12

In the same way, *N*,*N*-diisopropyl-1-naphthamide **10** (1.75 g, 6.9 mmol) and trimethylsilyl chloride (1.74 ml, 13.7 mmol) gave a crude product which was recrystallised from ethyl acetate to give the *amide* **12** as needles (1.70 g, 76%), mp 156.9–157.5 °C; ν_{max}(film)/cm^{-1} 2969, 2363, 2766, 1628, 1454, 1438, 1323 and 1041; δ_H(250 MHz; $CDCl_3$) 7.9–7.3 (6 H, m, Ar), 3.64 (1 H, septet, *J* 7, NCH), 3.49 (1 H, septet, *J* 7, NCH), 1.83 (3 H, d, *J* 7), 1.70 (3 H, d, *J* 7), 1.13 (3 H, d, *J* 7), 0.92 (3 H, d, *J* 7) [(CH_3)$_2$CH × 4] and 0.41 (9 H, s, SiMe_3); δ_C(75 MHz; $CDCl_3$) 170.9 (C=O), 141.9, 133.7, 133.5, 130.9, 129.6, 127.9, 126.9, 126.6, 126.1, 125.5 (Ar), 51.0, 46.4 (NCH × 2), 21.2, 20.6, 20.5, 20.2 (CHMe_2 × 2) and 0.9 (SiMe_3) (Found: C, 73.7; H, 8.81; N, 4.22%; M$^+$, 327.2012. $C_{20}H_{29}NOSi$ requires C, 73.3; H, 8.92; N, 4.28%; *M*, 327.2018).

_N,N_-Diethyl-2-methyl-1-naphthamide 14

In the same way, *N*,*N*-diethyl-1-naphthamide **13** (0.40 g, 1.8 mmol) and methyl iodide (2.5 mmol) gave a crude product which was purified by flash chromatography and then reversed-phase preparative HPLC (methanol–water) to give the *amide* **14** as an oil (0.119 g, 30%). ν_{max}(film)/cm^{-1} 1626 (C=O); δ_H(250 MHz; $CDCl_3$) 7.9–7.3 (6 H, m, ArH), 3.86 (1 H, dq, *J* 13 and 7, NCH_AH$_B$Me), 3.73 (1 H, dq, *J* 14 and 7, NCH$_A$$H_B$Me), 3.13 (2 H, q, *J* 7, NCH_2Me), 2.45 (3 H, s, ArCH_3), 1.42 (3 H, t, *J* 7) and 0.98 (3 H, t, *J* 7) [N(CH$_2$CH_3)$_2$]; δ_C(75 MHz; $CDCl_3$) 169.9 (C=O), 133.4, 131.6, 131.3, 129.8, 128.4, 128.2, 128.0, 126.8, 125.4, 124.5 (Ar), 42.7, 38.7 (2 × NCH_2), 19.4 (ArCH_3), 14.1 and 13.0 (2 × CH_2CH_3); *m*/*z* (CI) 242 (100%, M + H) (Found: M$^+$, 241.1467. $C_{16}H_{19}NO$ requires *M*, 241.1467).

_N,N_-Diethyl-2-trimethylsilyl-1-naphthamide 15

In the same way, *N*,*N*-diethyl-1-naphthamide **13** (0.40 g, 1.8 mmol) and trimethylsilyl chloride (2.5 mmol) gave a crude product which was purified by flash chromatography and then reversed-phase preparative HPLC (acetonitrile–water), yielding the *amide* **15** as an oil (0.252 g, 53%); ν_{max}(film)/cm^{-1} 1630 (C=O); δ_H(250 MHz; $CDCl_3$) 7.9–7.3 (6 H, m, ArH), 3.90 (1 H, dq, *J* 13 and 7, NCH_AH$_B$Me), 3.43 (1 H, dq, *J* 14 and 7, NCH$_A$$H_B$Me), 3.13 (2 H, ABX$_3$ m, NCH_2Me), 1.45 (3 H, t, *J* 7), 0.95 (3 H, t, *J* 7) [N(CH$_2$CH_3)$_2$] and 0.35 (9 H, s, SiMe_3); δ_C(75 MHz; $CDCl_3$) 170.8 (C=O), 140.9, 134.1, 133.4, 130.6, 129.4, 128.1, 127.3, 126.6, 124.9, 124.5 (Ar), 43.7, 39.1 (2 × NCH_2), 30.1 (SiMe_3), 13.8 and 13.0 (2 × CH_2CH_3); *m*/*z* (CI) 300 (100%, M + H) (Found: M$^+$, 299.1705. $C_{18}H_{25}NOSi$ requires *M*, 299.1705).

(_R_$_a$*,1′_R_*)- and (_R_$_a$*,1′_S_*)-_N,N_-Diisopropyl-2-(1′-hydroxyethyl)-1-naphthamide 16b and 16a (R = Me)

sec-Butyllithium (3.4 ml of a 1.3 M solution in cyclohexane) was added to a stirred solution of *N*,*N*-diisopropyl-1-naphthamide **10** (1.02 g, 4 mmol) in dry THF (60 ml) under nitrogen at −78 °C. After 30 min, freshly distilled acetaldehyde (1 ml) was added to the yellow–sepia solution. The mixture was stirred for a further 30 min at −78 °C then allowed to warm to −20 °C. After 30 min, freshly distilled acetaldehyde (1 ml) was added to the yellow–sepia solution. The mixture was stirred for a further 30 min at −78 °C then allowed to warm to −20 °C. Saturated aqueous ammonium chloride was added and a small aliquot removed from the organic layer and transferred to a freezer at −18 °C. Analytical HPLC of this sample showed a 15:85 ratio for diastereoisomers. The remainder of the mixture was diluted with water and extracted with CH_2Cl_2 (×3). The combined organic fractions were washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure at a temperature not exceeding 30 °C. The crude product was purified by flash chromatography [1:1 petrol (bp 60–80 °C)–EtOAc then EtOAc] to give 1.095 g (92%) of a 21:79 mixture of atropisomers. Separation by preparative HPLC (1:1 hexane–EtOAc) gave (R$_a$*,1′R*)-N,N-*diisopropyl*-2-(1′-*hydroxyethyl*)-1-*naphthamide* **16b** (R = Me) as a white solid, mp 146–148 °C; R_f (EtOAc) 0.57; t_r (2:1 hexane–EtOAc) 13.3 min; ν_{max}(film)/cm^{-1} 3402 (OH) and 1609 (C=O); δ_H(300 MHz; $CDCl_3$) 7.9–7.4 (6 H, m, ArH), 5.11 (1 H, q, *J* 6.5, C*H*OH), 3.61 (2 H, m, 2 × NCH), 1.78 (3 H, d, *J* 7.0), 1.69 (3 H, d, *J* 7.0), 1.56 (3 H, d, *J* 6.5), 1.11 (3 H, d, *J* 7.0) and 1.00 (3 H, d, *J* 7.0) (5 × CH_3); δ_C(75 MHz; $CDCl_3$) 169.1 (C=O), 138.3, 132.8, 132.5, 129.3, 128.7, 128.1, 126.7, 126.1, 125.0, 123.1 (Ar), 68.1 (CHOH), 51.2, 46.2 (2 × NCH), 25.7, 20.9, 20.7, 20.6 and 20.5 (5 × CH_3); *m*/*z* (CI) 300 (100%, M + H) (Found: M$^+$, 299.1962. $C_{19}H_{25}NO_2$ requires *M*, 299.1963).

Also obtained was (R$_a$*,1′S*)-N,N-*diisopropyl*-2-(1′-*hydroxyethyl*)-1-*naphthamide* **16a** (R = Me) as a white solid, mp 113–114 °C; R_f (EtOAc) 0.54; t_r (2:1 hexane–EtOAc) 24.4 min; ν_{max}(film)/cm^{-1} 3427 (OH) and 1609 (C=O); δ_H(300 MHz; $CDCl_3$) 7.9–7.4 (6 H, m, ArH), 5.10 (1 H, q, *J* 7, C*H*OH), 3.68 (1 H, septet, *J* 7), 3.59 (1 H, septet, *J* 7) (2 × NCH), 3.55 (1 H, br s, OH), 1.80 (3 H, d, *J* 7), 1.76 (3 H, d, *J* 7), 1.68 (3 H, d, *J* 7), 1.12 (3 H, d, *J* 7) and 1.10 (3 H, d, *J* 7) (5 × CH_3); δ_C(75 MHz; $CDCl_3$) 170.1 (C=O), 138.1, 133.9, 132.8, 129.2, 128.8, 128.2, 126.8, 126.3, 124.9, 123.2, (Ar), 66.6 (CHOH), 51.4, 46.4 (2 × NCH), 21.3, 20.9, 20.6, 20.6 and 20.5 (5 × CH_3); *m*/*z* (CI) 300 (100%, M + H) (Found: M$^+$, 299.1963. $C_{19}H_{25}NO_2$ requires *M*, 299.1963).

(_R_$_a$*,1′_R_*)- and (_R_$_a$*,1′_S_*)-_N,N_-Diethyl-2-(1′-hydroxyethyl)-1-naphthamide 17b and 17a (R = Me)

In the same way, *N*,*N*-diethyl-1-diethyl-1-naphthamide **13** (0.91 g, 4 mmol) and acetaldehyde (1 ml) gave a crude product which was purified by flash chromatography [1:1 petrol (bp 60–80 °C)–EtOAc then EtOAc] to give a mixture of the two atropisomers **17b** and **17a** (R = Me) (0.726 g, 67%). Analytical HPLC (2:1 hexane–EtOAc) of the crude aliquot showed the atropisomers to be present in a ratio of 23:77; analytical HPLC of the purified material showed a ratio of 28:72. The chromatographed mixture was separated by preparative HPLC (1:1 hexane–EtOAc) to give (R$_a$,1′R*)-N,N-*diethyl*-2-(1′-*hydroxyethyl*)-1-*naphthamide* **17b** (R = Me) as a white solid, mp 132–134 °C; R_f (EtOAc) 0.40; t_r (2:1 hexane–EtOAc) 24.6 min; ν_{max}(film)/cm^{-1} 3417 (OH) and 1610 (C=O); δ_H(300 MHz; $CDCl_3$) 8.0–7.4 (6 H, m, ArH), 5.04 (1 H, q, *J* 6.5, C*H*OH), 3.73 (2 H, m), 3.10 (2 H, m) (2 × NCH_2), 2.72 (1 H, br s, OH), 1.56 [3 H, d, *J* 6.5, CH(OH)CH_3], 1.40 (3 H, t, *J* 7.5) and 0.96 (3 H, t, *J* 7.5) (2 × CH_2CH_3); δ_C(75 MHz; $CDCl_3$) 169.4 (C=O), 138.9, 132.8, 131.2, 129.3, 129.1, 128.2, 126.9, 126.2, 124.8,123.2 (Ar), 68.3 (CHOH), 43.2, 38.9 (2 × NCH_2), 25.7 [CH(OH)CH_3], 13.9 and 12.9 (2 × CH_2CH_3); *m*/*z* (CI) 272 (8%, M + H) and 254 (100,

M − OH) (Found: M^+, 271.1566. $C_{17}H_{21}NO_2$ requires *M*, 271.1572).

Also obtained was (R_a*,1′S*)-N,N-*diethyl*-2-(1′-*hydroxyethyl*)-1-*naphthamide* **17a** (R = Me) as a white solid, mp 115–118 °C; R_f (EtOAc) 0.40; t_r (2:1 hexane–EtOAc) 27.4 min; ν_{max}(film)/cm^{-1} 3416 (OH), 1611 (C=O); δ_H(300 MHz; $CDCl_3$) 8.0–7.4 (6 H, m, ArH), 5.03 (1 H, q, *J* 6.5, C*H*OH), 3.76 (2 H, m), 3.09 (2 H, m) (2 × NCH_2), 1.60 [3 H, d, *J* 6.5, CH(OH)CH_3], 1.43 (3 H, t, *J* 7.5) and 1.00 (3 H, t, *J* 7.5) (2 × CH_2CH_3); δ_C(75 MHz; $CDCl_3$) 170.1 (C=O), 139.1, 132.7, 132.1, 129.2, 129.1, 128.3, 127.0, 126.3, 124.7, 123.3 (Ar), 66.7 (CHOH), 43.3, 38.9 (2 × NCH_2), 22.1 [CH(OH)*C*H$_3$], 13.8 and 12.8 (2 × CH_2CH_3); *m*/*z* (CI) 272 (9%, M + H) and 254 (100, M − OH) (Found: M^+, 271.1567. $C_{17}H_{21}NO_2$ requires *M*, 271.1572).

(*R*$_a$*,1′*R**)- and (*R*$_a$*,1′*S**)-*N*,*N*-Diisopropyl-2-(1′-hydroxypropyl)-1-naphthamide 16b and 16a (R = Et)

In the same way, *N*,*N*-diisopropyl-1-naphthamide **10** (1.02 g, 4 mmol) and propionaldehyde gave a 10:90 mixture of atropisomers **16b** and **16a** (R = Et), which was purified by flash chromatography [1:1 petrol (bp 60–80 °C)–EtOAc] to give 0.993 g (79%) of a 22:78 mixture of atropisomers. Separation by preparative HPLC (1:1 hexane–EtOAc) gave (R_a*,1′R*)-N,N-*diisopropyl*-2-(1′-*hydroxypropyl*)-1-*naphthamide* **16b** (R = Et) as a white solid, mp 148–150 °C; R_f [1:1 petrol (bp 60–80 °C)–EtOAc] 0.47; t_r (2:1 hexane–EtOAc) 4.3 min; ν_{max}(film)/cm^{-1} 3355 (OH) and 1609 (C=O); δ_H(200 MHz; $CDCl_3$) 7.8–7.4 (6 H, m, ArH), 4.74 (1 H, t, *J* 7, C*H*OH), 3.57 (1 H, septet, *J* 7), 3.55 (1 H, septet, *J* 7) (2 × NCH), 2.70 (1 H, br s, OH), 1.75 (2 H, m, CH_2Me), 1.73 (3 H, d, *J* 7), 1.63 (3 H, d, *J* 7), 1.05 (3 H, d, *J* 7), 0.94 (3 H, d, *J* 7) [2 × CH(CH_3)$_2$] and 0.91 (3 H, t, *J* 7, CH_2CH_3); δ_C(75 MHz; $CDCl_3$) 169.5 (C=O), 137.8, 133.5, 133.3, 129.8, 128.9, 128.5, 127.1, 126.6, 125.6, 123.9 (Ar), 73.8 (CHOH), 51.6, 46.7 (2 × NCH), 32.2 (*C*H$_2$Me), 21.4, 21.1, 21.0, 20.8 [2 × CH(*C*H$_3$)$_2$] and 11.0 (CH_2CH_3); *m*/*z* (CI) 314 (30%, M + H) and 296 (100, M − OH) (Found: M^+, 313.2041. $C_{20}H_{27}NO_2$ requires *M*, 313.2042).

Also obtained was (R_a*,1′S*)-N,N-*diisopropyl*-2-(1′-*hydroxypropyl*)-1-*naphthamide* **16a** (R = Et) as an oil, R_f [1:1 petrol (bp 60–80 °C)–EtOAc] 0.47; t_r (2:1 hexane–EtOAc) 6.5 min; ν_{max}(film)/cm^{-1} 3410 (OH) and 1605 (C=O); δ_H(200 MHz; $CDCl_3$) 7.9–7.4 (6 H, m, ArH), 4.76 (1 H, dd, *J* 8, 5, C*H*OH), 3.65 (2 H, septet, *J* 7, 2 × NCH), 3.60 (1 H, br s, OH), 1.85 (2 H, m, CH_2Me), 1.80 (3 H, d, *J* 7), 1.73 (3 H, d, *J* 7) {N[CH(CH_3)$_2$]^X}, 1.13 (3 H, t, *J* 7, CH_2CH_3), 1.11 (3 H, d, *J* 7) and 1.09 (3 H, d, *J* 7) {N[CH(CH_3)$_2$]^Y}; δ_C(75 MHz; $CDCl_3$) 171.5 (C=O), 135.9, 129.4, 128.8, 128.7, 127.2, 127.0, 126.8, 126.6, 125.4, 124.2 (Ar), 73.0 (CHOH), 52.0, 47.0 (2 × NCH), 29.3 (*C*H$_2$Me), 21.3, 21.1, 21.0, 20.9 [2 × CH(*C*H$_3$)$_2$] and 11.80 (CH_2CH_3); *m*/*z* (CI) 314 (25%, M + H) and 296 (100, M − OH) (Found: M^+, 313.2039. $C_{20}H_{27}NO_2$ requires *M*, 313.2042).

(*R*$_a$*,1′*R**)- and (*R*$_a$*,1′*S**)-*N*,*N*-Diethyl-2-(1′-hydroxypropyl)-1-naphthamide 17b and 17a (R = Et)

In the same way, *N*,*N*-diethyl-1-naphthamide **13** (0.91 g, 4 mmol) and propionaldehyde gave a 22:78 mixture of atropisomers **17b** and **17a** (R = Et), which was purified by flash chromatography [2:1 then 1:1 petrol (bp 60–80 °C)–EtOAc] to give 0.866 g (76%) of a 28:78 mixture of atropisomers. Separation by preparative HPLC (1:1 hexane–EtOAc) gave (R_a*,1′R*)-N,N-*diethyl*-2-(1′-*hydroxypropyl*)-1-*naphthamide* **17b** (R = Et) as a white solid, mp 117–120 °C; R_f [1:1 petrol (bp 60–80 °C)–EtOAc] 0.24; t_r (2:1 hexane–EtOAc) 11.7 min; ν_{max}(film)/cm^{-1} 3410 (OH) and 1608 (C=O); δ_H(200 MHz; $CDCl_3$) 7.9–7.4 (6 H, m, ArH), 4.68 (1 H, dd, *J* 8, 6, C*H*OH), 3.74 (2 H, m), 3.07 (2 H, q, *J* 7) (2 × NCH_2), 1.90 [2 H, m, CH(OH)CH_2Me], 1.38 (3 H, t, *J* 7.5), 1.01 (3 H, t, *J* 7.5) and 0.97 (3 H, t, *J* 7) (3 × CH_2CH_3); δ_C(75 MHz; $CDCl_3$) 170.2 (C=O), 138.8, 129.7, 129.5, 128.9, 128.8, 128.7, 127.4, 126.8, 125.2, 124.2 (Ar), 73.0 (CHOH), 43.7, 39.2 (2 × NCH_2), 29.3 [CH(OH)*C*H$_2$Me], 14.2, 13.3 and 11.4 (3 × CH_2CH_3); *m*/*z* (CI) 286 (15%, M + H), 268 (100, M − OH) and 213 (60, M − NEt_2) (Found: M^+, 285.1726. $C_{18}H_{23}NO_2$ requires *M*, 285.1729).

Also obtained was (R_a*,1′S*)-N,N-*diethyl*-2-(1′-*hydroxypropyl*)-1-*naphthamide* **17a** (R = Et) as an oil; R_f [1:1 petrol (bp 60–80 °C)–EtOAc] 0.24; t_r (2:1 hexane–EtOAc) 15.4 min; ν_{max}(film)/cm^{-1} 3410 (OH) and 1606 (C=O); δ_H(200 MHz; $CDCl_3$) 7.9–7.4 (6 H, m, ArH), 4.71 (1 H, dd, *J* 8, 6, C*H*OH), 3.76 (2 H, q, *J* 7), 3.40 (1 H, br s, OH), 3.09 (2 H, q, *J* 7) (2 × NCH_2), 1.90 [2 H, m, CH(OH)CH_2Me], 1.38 (3 H, t, *J* 7), 1.04 (3 H, t, *J* 7.5) and 0.99 (3 H, t, *J* 7) (3 × CH_2CH_3); *m*/*z* (CI) 286 (8%, M + H), 268 (35, M − OH) and 213 (100, M − NEt_2) (Found: M^+, 285.1735. $C_{18}H_{23}NO_2$ requires *M*, 285.1729).

(*R*$_a$*,1′*R**)- and (*R*$_a$*,1′*S**)-*N*,*N*-Diisopropyl-2-(1′-hydroxyhexyl)-1-naphthamide 16b and 16a (R = *n*-C_5H_{11})

In the same way, *N*,*N*-diisopropyl-1-naphthamide **10** (0.255 g, 1 mmol) and hexanal (0.2 ml) gave an 18:82 mixture of atropisomers **16b** and **16a** (R = *n*-C_5H_{11}), which was purified by flash chromatography [1:1 petrol (bp 60–80 °C)–EtOAc] to give 0.266 g (75%) of a mixture of atropisomers. Separation by preparative HPLC (4:1 hexane–EtOAc) gave (R_a*,1′R*)-N,N-*diisopropyl*-2-(1′-*hydroxyhexyl*)-1-*naphthamide* **16b** (R = *n*-C_5H_{11}) as a white solid, mp 98–103 °C; R_f [2:1 petrol (bp 60–80 °C)–EtOAc] 0.43; t_r (4:1 hexane–EtOAc) 4.6 min; ν_{max}(film)/cm^{-1} 3350 (OH) and 1609 (C=O); δ_H(200 MHz; $CDCl_3$) 7.9–7.4 (6 H, m, ArH), 4.84 (1 H, dd, *J* 8, 6, C*H*OH), 3.57 (2 H, septet, 2 × NCH), 2.45 (1 H, br s, OH), 1.85 (2 H, m, CHOHCH_2), 1.83 (3 H, d, *J* 7), 1.65 (3 H, d, *J* 7) {N[CH(CH_3)$_2$]^X}, 1.25 [6 H, m, (CH_2)$_3$], 1.07 (3 H, d, *J* 7), 1.05 (3 H, d, *J* 7) {N[CH(CH_3)$_2$]^Y} and 0.84 (3 H, t, *J* 7, CH_2CH_3); δ_C(75 MHz; $CDCl_3$) 169.5 (C=O), 138.0, 129.0, 128.8, 128.7, 128.5, 127.1, 126.7, 125.8, 125.6, 123.9 (Ar), 72.3 (CHOH), 51.6, 46.6 (2 × NCH), 39.6, 32.0, 26.1, 23.0 [(CH$_2$)$_4$], 21.4, 21.3, 21.2, 21.1 [2 × CH(*C*H$_3$)$_2$] and 14.6 (CH_2CH_3); *m*/*z* (CI) 356 (10%, M + H), 338 (95, M − OH) and 256 (100, M + H − NPr^i_2) (Found: M^+, 335.2518. $C_{23}H_{33}NO_2$ requires *M*, 355.2511).

Also obtained was (R_a*,1′S*)-N,N-*diisopropyl*-2-(1′-*hydroxyhexyl*)-1-*naphthamide* **16a** (R = *n*-C_5H_{11}) as an oil, R_f [1:1 petrol (bp 60–80 °C)–EtOAc] 0.45; t_r (4:1 hexane–EtOAc) 9.1 min; ν_{max}(film)/cm^{-1} 3450 (OH) and 1606 (C=O); δ_H(200 MHz; $CDCl_3$) 7.9–7.4 (6 H, m, ArH), 4.80 (1 H, dd, *J* 9, 3, C*H*OH), 3.59 (2 H, septet, 2 × NCH), 2.60 (1 H, br s, OH), 1.75 (2 H, m, CHOHCH_2), 1.74 (3 H, d, *J* 7), 1.69 (3 H, d, *J* 7) {N[CH)CH_3)$_2$]^X}, 1.35 [6 H, m, (CH_2)$_3$], 1.06 (3 H, d, *J* 7), 1.04 (3 H, d, *J* 7) {N[CH(CH_3)$_2$]^Y} and 0.90 (3 H, t, *J* 7, CH_2CH_3); δ_C(75 MHz; $CDCl_3$) 171.8 (C=O), 138.0, 136.2, 135.0, 133.0, 129.3, 128.7, 127.2, 126.8, 125.3, 124.3 (Ar), 71.3 (CHOH), 51.9, 47.0 (2 × NCH), 36.1, 32.4, 27.0, 23.1 [(CH$_2$)$_4$], 21.3, 21.1, 20.9, 20.8 [2 × CH(*C*H$_3$)$_2$] and 14.6 (CH_2CH_3); *m*/*z* (CI) 356 (10%, M + H) and 338 (100, M − OH) (Found: M^+, 335.2507. $C_{23}H_{33}NO_2$ requires *M*, 355.2511).

(*R*$_a$*,1′*R**)- and (*R*$_a$*,1′*S**)-*N*,*N*-Diethyl-2-(1′-hydroxyhexyl)-1-naphthamide 17b and 17a (R = *n*-C_5H_{11})

In the same way, *N*,*N*-diethyl-1-naphthamide **13** (0.227 g, 1 mmol) and hexanal (0.2 ml) gave a 23:77 mixture of atropisomers **17b** and **17a** (R = *n*-C_5H_{11}), which was purified by flash chromatography [1:1 petrol (bp 60–80 °C)–EtOAc] to give 0.278 g (85%) of a 28:72 mixture of atropisomers. Separation by preparative HPLC (1:1 hexane–EtOAc) gave (R_a*,1′R*)-N,N-*diethyl*-2-(1′-*hydroxyhexyl*)-1-*naphthamide* **17b** (R = *n*-C_5H_{11}) as a white solid, mp 67–72 °C; R_f [2:1 petrol (bp 60–80 °C)–EtOAc] 0.29; t_r (2:1 hexane–EtOAc) 4.6 min; ν_{max}(film)/cm^{-1} 3355 (OH) and 1609 (C=O); δ_H(200 MHz; $CDCl_3$) 7.9–7.4 (6 H, m, ArH), 4.86 (1 H, dd, *J* 8, 6, C*H*OH), 3.58 (2 H, m), 2.89 (2 H, m) (2 × NCH_2), 1.78 [2 H, m, CH(OH)CH_2], 1.25 [6 H, m, (CH_2)$_3$Me], 1.20 (3 H, t, *J* 7.5), 1.07 (3 H, t, *J* 7.5) and 0.97 (3 H, t, *J* 7) (3 × CH_2CH_3); δ_C(75 MHz; $CDCl_3$) 170.1 (C=O), 134.8, 129.1, 128.8, 128.6, 127.2, 127.0, 126.9, 126.7,

125.6, 123.9 (Ar), 72.5 (CHOH), 51.7, 46.7 (2 × NCH_2), 39.6, 32.0, 26.2, 23.1 [$(CH_2)_4$], 21.5, 21.1 and 14.6 (3 × CH_3).

Also obtained was (R_a*,1′S*)-N,N-*diethyl*-2-(1′-*hydroxyhexyl*)-1-*naphthamide* **17a** (R = *n*-C_5H_{11}) as an oil; R_f [2:1 petrol (bp 60–80 °C)–EtOAc] 0.29; t_r (2:1 hexane–EtOAc) 6.8 min; ν_{max}(film)/cm^{-1} 3340 (OH) and 1609 (C=O); δ_H(200 MHz; $CDCl_3$) 7.9–7.4 (6 H, m, ArH), 4.76 (1 H, dd, *J* 9, 3, C*H*OH), 3.56 (2 H, m), 2.90 (2 H, m) (2 × NCH_2), 1.65 [2 H, m, CH(OH)CH_2], 1.35 [6 H, m, $(CH_2)_3$Me], 1.10 (3 H, t, *J* 7.5), 1.07 (3 H, t, *J* 7.5) and 0.95 (3 H, t, *J* 7) (3 × CH_2CH_3); δ_C(75 MHz; $CDCl_3$) 171.1 (C=O), 134.6, 129.1, 128.5, 128.4, 127.2, 127.0, 126.9, 126.7, 125.56, 123.79 (Ar), 71.5 (CHOH), 51.6, 46.8 (2 × NCH_2), 39.5, 32.0, 26.2, 22.1 [$(CH_2)_4$], 21.4, 21.0 and 13.9 (3 × CH_3).

(R_a*,1′*R**)- and (R_a*,1′*S**)-*N*,*N*-Diisopropyl-2-(1′-hydroxy-2′-methylpropyl)-1-naphthamide 16b and 16a (R = Pr^i)

In the same way, *N*,*N*-diisopropyl-1-naphthamide **10** (1.02 g, 4 mmol) and isobutyraldehyde gave a 23:77 mixture of atropisomers **16b** and **16a** (R = Pr^i), which was purified by flash chromatography [4:1 petrol (bp 60–80 °C)–EtOAc then EtOAc] to give 1.192 g (91%) of a mixture of atropisomers. Separation by preparative HPLC (4:1 hexane–EtOAc) gave (R_a*,1′R*)-N,N-*diisopropyl*-2-(1′-*hydroxy*-2′-*methylpropyl*)-1-*naphthamide* **16b** (R = Pr^i) as a white solid, mp 136–139 °C; R_f [1:1 petrol (bp 60–80 °C)–EtOAc] 0.65; t_r (4:1 hexane–EtOAc) 5.3 min; ν_{max}(film)/cm^{-1} 3410 (OH) and 1607 (C=O); δ_H(200 MHz; $CDCl_3$) 7.9–7.4 (6 H, m, ArH), 4.50 (1 H, d, *J* 7.5, C*H*OH), 3.59 (1 H, septet, *J* 7), 3.55 (1 H, septet, *J* 7) (2 × NCH), 2.45 (1 H, br s, OH), 2.12 [2 H, octet, *J* 7, CH(OH)C*H*Me$_2$], 1.75 (3 H, d, *J* 7), 1.65 (3 H, d, *J* 7), 1.09 (63 H, d, *J* 7), 1.05 (3 H, d, *J* 7), 0.95 (3 H, d, *J* 7) and 0.80 (3 H, d, *J* 7) (6 × CH_3); δ_C(75 MHz; $CDCl_3$) 169.4 (C=O), 136.9, 134.2, 133.3, 129.9, 128.8, 128.5, 127.1, 126.7, 125.7, 124.2 (Ar), 77.9 (CHOH), 51.5, 46.6 (2 × NCH), 35.7 [CH(OH)*C*HMe$_2$], 21.5, 21.2, 21.1, 20.8, 20.1 and 18.7 (6 × CH_3); *m*/*z* (CI) 328 (25%, M + H) and 310 (100, M − OH) (Found: M$^+$, 327.2203. $C_{21}H_{29}NO_2$ requires *M*, 327.2198).

Also obtained was (R_a*,1′S*)-N,N-*diisopropyl*-2-(1′-*hydroxy*-2′-*methylpropyl*)-1-*naphthamide* **16a** (R = Pr^i) as a white solid, mp 136–139 °C; R_f [1:1 petrol (bp 60–80 °C)–EtOAc] 0.65; t_r (4:1 hexane–EtOAc) 6.8 min; ν_{max}(film)/cm^{-1} 3410 (OH) and 1608 (C=O) δ_H(200 MHz; $CDCl_3$) 7.9–7.4 (6 H, m, ArH), 4.39 (1 H, d, *J* 9.5, C*H*OH), 3.65 (2 H, septet, *J* 7, 2 × NCH), 3.20 (1 H, br s, OH), 2.42 [2 H, dseptet, *J* 9.5, 7, CH(OH)C*H*Me$_2$], 1.75 (3 H, d, *J* 7), 1.70 (3 H, d, *J* 7), 1.22 (3 H, d, *J* 7), 1.08 (6 H, d, *J* 7) and 0.88 (3 H, d, *J* 7) (6 × CH_3); δ_C(75 MHz; $CDCl_3$) 170.3 (C=O), 137.5, 135.8, 133.1, 132.9, 129.2, 128.7, 127.1, 126.8, 125.3, 124.5 (Ar), 76.9 (CHOH), 51.9, 46.9 (2 × NCH), 31.5 [CH(OH)*C*HMe$_2$], 21.6, 21.1, 21.0, 20.9, 20.4 and 20.2 (6 × CH_3); *m*/*z* (CI) 328 (15%, M + H) and 310 (100, M − OH) (Found: M$^+$, 327.2192. $C_{21}H_{29}NO_2$ requires *M*, 327.2198).

(R_a*,1′*R**)- and (R_a*,1′*S**)-*N*,*N*-Diethyl-2-(1′-hydroxy-2′-methylpropyl)-1-naphthamide 17b and 17a (R = Pr^i)

In the same way, *N*,*N*-diethyl-1-naphthamide **13** (0.227 g, 1 mmol) and isobutyraldehyde gave a 30:70 mixture of atropisomers **17b** and **17a** (R = Pr^i), which was purified by flash chromatography [2:1 then 1:1 petrol (bp 60–80 °C)–EtOAc] to give 0.254 g (85%) of a mixture of atropisomers. Separation by preparative HPLC (1:1 hexane–EtOAc) gave (R_a*,1′R*)-N,N-*diethyl*-2-(1′-*hydroxy*-2′-*methylpropyl*)-1-*naphthamide* **17b** (R = Pr^i) as a white solid, mp 146–149 °C; R_f [1:1 petrol (bp 60–80 °C)–EtOAc] 0.40; t_r (2:1 hexane–EtOAc 6.5 min; ν_{max}(film)/cm^{-1} 3400 (OH) and 1608 (C=O); δ_H(200 MHz; $CDCl_3$) 7.9–7.4 (6 H, m, ArH), 4.40 (1 H, d, *J* 7, C*H*OH), 3.75 [1 H, dq, *J* 14, 7, N(CH_AH$_B$)^X], 3.63 [1 H, dq, *J* 14, 7, N(CH$_A$$H_B$)^X], 3.06 [2 H, ABX$_3$ m, N(CH$_2$)^Y], 2.50 (1 H, br s, OH), 2.10 [2 H, octet, CH(OH)C*H*Me$_2$], 1.37 [3 H, t, *J* 7.5, N(CH$_2$CH_3)^X], 1.03 (3 H, d, *J* 7, CH*Me*$_A$Me$_B$), 0.91 [3 H, t, *J* 7.5, N(CH$_2$CH_3)^Y] and 0.76 (3 H, d, *J* 7, CHMe$_A$*Me*$_B$); δ_C(75 MHz; $CDCl_3$) 169.7 (C=O), 137.6, 133.2, 132.9, 130.0, 129.2, 128.6, 127.4, 126.7, 125.6, 124.5 (Ar), 78.1 (CHOH), 43.6, 39.4 (2 × NCH_2), 35.5 (*C*HMe$_2$), 20.1, 18.9, 14.5 and 13.3 (4 × CH_3); *m*/*z* (CI) 300 (20%, M + H), 282 (75, M − OH) and 227 (100, M − NEt_2) (Found: M$^+$, 299.1885. $C_{18}H_{23}NO_2$ requires *M*, 299.1885).

Also obtained was (R_a*,1′S*)-N,N-*diethyl*-2-(1′-*hydroxy*-2′-*methylpropyl*)-1-*naphthamide* **17b** (R = Pr^i) as a white solid, mp 136–142 °C; R_f [1:1 petrol (bp 60–80 °C)–EtOAc] 0.40; t_r (2:1 hexane–EtOAc) 9.4 min; ν_{max}(film)/cm^{-1} 3410 (OH) and 1605 (C=O); δ_H(200 MHz; $CDCl_3$) 7.9–7.4 (6 H, m, ArH), 4.35 (1 H, d, *J* 9, C*H*OH), 3.83 [1 H, dq, *J* 14, 7, N(CH_AH$_B$)^X], 3.75 [1 H, dq, *J* 14, 7, N(CH$_A$$H_B$)^X], 3.20 (1 H, br s, OH), 3.08 [2 H, q, *J* 7, N(CH$_2$)^Y], 2.26 [2 H, octet, CH(OH)C*H*Me$_2$], 1.38 [3 H, t, *J* 7, N(CH$_2$CH_3)^X], 1.08 (3 H, d, *J* 7, CH*Me*$_A$Me$_B$), 1.01 [3 H, t, *J* 7, N(CH$_2$CH_3)^Y] and 0.80 (3 H, d, *J* 7, CHMe$_A$*Me*$_B$); δ_C(75 MHz; $CDCl_3$) 170.5 (C=O), 138.5, 134.0, 133.0, 129.9, 129.6, 128.7, 127.3, 126.8, 125.2, 124.7 (Ar), 77.9 (CHOH), 43.8, 38.9 (2 × NCH_2), 32.6 (*C*HMe$_2$), 20.4, 20.0, 14.1 and 13.3 (4 × CH_3); *m*/*z* (CI) 300 (15%, M + H), 282 (85, M − OH) and 227 (100, M − NEt_2) (Found: M$^+$, 299.1886. $C_{18}H_{23}NO_2$ requires *M*, 299.1885).

(R_1*,α*R**)- and (R_a*,α*S**)-*N*,*N*-Diisopropyl-2-(α-hydroxybenzyl)-1-naphthamide 16b and 16a (R = Ph)

In the same way, *N*,*N*-diisopropyl-1-naphthamide **10** (1.02 g, 4 mmol) and benzaldehyde (0.5 ml) gave a 72:28 mixture of atropisomers **16b** and **16a** (R = Ph), which was purified by flash chromatography [3:2 then 1:1 petrol (bp 60–80 °C)–EtOAc] to give 1.28 g (89%) of a mixture of atropisomers. Separation by preparative HPLC (4:1 hexane–EtOAc) gave (R_a*,αR*)-N,N-*diisopropyl*-2-(α-*hydroxybenzyl*)-1-*naphthamide* **16b** (R = Ph) as a white solid, mp 169–171 °C; R_f [2:1 petrol (bp 40–60 °C)–EtOAc] 0.42; t_r (4:1 hexane–EtOAc) 8.3 min; ν_{max}(film)/cm^{-1} 3350 (OH) and 1606 (C=O); δ_H(300 MHz; $CDCl_3$) 8.0–7.1 (11 H, m, ArH), 6.12 (1 H, br s, C*H*OH), 3.72 (1 H, septet, *J* 7), 3.68 (1 H, septet, *J* 7) (2 × NCH), 2.87 (1 H, br s, OH), 1.83 (3 H, d, *J* 7), 1.74 (3 H, d, *J* 7), 1.16 (3 H, d, *J* 7) and 1.06 (3 H, d, *J* 7) (4 × CH_3); δ_C(75 MHz; $CDCl_3$) 169.2 (C=O), 143.7, 136.4, 133.7, 132.9, 129.4, 128.8, 128.4, 128.1, 127.2, 126.8, 126.5, 125.8, 125.4, 124.7 (Ar), 73.1 (CHOH), 51.4, 46.3 (2 × NCH), 20.9, 20.7, 20.6 and 20.5 (4 × CH_3); *m*/*z* (CI) 362 (100%, M + H) and 344 (Found: M$^+$, 361.2048. $C_{22}H_{27}NO_2$ requires *M*, 361.2042).

Also obtained was (R_a*,αS*)-N,N-*diisopropyl*-2-(α-*hydroxybenzyl*)-1-*naphthamide* **16a** (R = Ph) as a sticky white solid, R_f [2:1 petrol (bp 40–60 °C)–EtOAc] 0.39; t_r (4:1 hexane–EtOAc) 17.9 min; ν_{max}(film)/cm^{-1} 3418 (OH) and 1606 (C=O); δ_H(300 MHz; $CDCl_3$) 7.9–7.1 (11 H, m, ArH), 6.17 (1 H, s, C*H*OH), 3.3–3.1 (2 H, m, 2 × NCH), 1.83 (3 H, d, *J* 7), 1.76 (3 H, d, *J* 7), 1.18 (3 H, d, *J* 7) and 1.07 (3 H, d, *J* 7) (4 × CH_3); δ_C(75 MHz; $CDCl_3$) 170.4 (C=O), 141.5, 137.9, 135.0, 132.8, 129.1, 128.7, 128.3, 127.4, 127.0, 126.9, 126.6, 125.7, 124.9 (Ar), 72.7 (CHOH), 51.7, 46.6 (2 × NCH), 21.0, 20.7, 20.6 and 20.5 (4 × CH_3); *m*/*z* (CI) 362 (8%, M + H), 346 and 344 (Found: M$^+$, 361.2048. $C_{22}H_{27}NO_2$ requires *M*, 361.2042).

(R_a*,α*R**)- and (R_a*,α*S**)-*N*,*N*-Diethyl-2-(α-hydroxybenzyl)-1-naphthamide 17b and 17a (R = Ph)

In the same way, *N*,*N*-diethyl-1-naphthamide **13** (0.91 g, 4 mmol) and benzaldehyde (0.5 ml) gave a 51:49 mixture of atropisomers **17b** and **17a** (R = Ph) which was crystallised from ethyl acetate to give almost pure **17a** (R = Ph) (0.261 g, 20%). The mother liquors were purified by flash chromatography [3:2 then 1:1 petrol (bp 60–80 °C)–EtOAc] to give a further 0.872 g (65%) of a mixture of atropisomers. Separation by preparative HPLC (4:1 hexane–EtOAc) gave (R_a*,αR*)-N,N-*diethyl*-2-(α-*hydroxybenzyl*)-1-*naphthamide* **17b** (R = Ph) as a white solid, mp 141–143 °C; R_f (EtOAc) 0.63; t_r (4:1 hexane–EtOAc) 11.7 min; ν_{max}(film)/cm^{-1} 3416 (OH) and 1610 (C=O); δ_H(300 MHz; $CDCl_3$) 8.0–7.1 (11 H, m, ArH), 6.03 (1 H, br s, C*H*OH), 3.75 [1 H, m, N(CH_AH$_B$)^X], 3.70 (1 H, br s, OH), 3.52 [1 H, m,

N(CH_AH_B)^X], 3.02 [1 H, m, N(CH_AH_B)^Y], 2.77 [H, dq, *J* 14 and 7, N(CH_AH_B)^Y], 1.38 (3 H, t, *J* 7) and 0.92 (3 H, t, *J* 7) (2 × CH_3); δ_C(75 MHz; $CDCl_3$) 169.7 (C=O), 143.5, 137.9, 132.7, 132.6, 129.6, 129.3, 128.2, 128.1, 127.1, 127.0, 126.5, 125.8, 125.7 (Ar), 74.7 (CHOH), 43.6, 39.2 (2 × CH_2), 13.6 and 13.0 (2 × CH_3); *m*/*z* (CI) 334 (100%, M + H) and 318 (M − CH_3) (Found: M^+, 333.1733. $C_{22}H_{23}NO_2$ requires *M*, 333.1729).

Also obtained was (R_a*,αS*)-N,N-*diethyl*-2-(α-*hydroxybenzyl*)-1-*naphthamide* **17a** (R = Ph) as a white solid, mp 125–127 °C; R_f (EtOAc) 0.58; t_r (4:1 hexane–EtOAc) 27.7 min; ν_{max}(film)/cm^{-1} 3414 (OH) and 1609 (C=O); δ_H(300 MHz; $CDCl_3$) 7.9–7.2 (11 H, m, ArH), 6.10 (1 H, s, C*H*OH), 4.00 (1 H, br s, OH), 3.81 [1 H, m, N(CH_AH_B)^X], 3.69 [1 H, m, N(CH_AH_B)^X], 2.99 [1 H, m, N(CH_AH_B)^Y], 2.88 [1 H, m, N(CH_AH_B)^Y], 1.95 (3 H, t, *J* 7) and 0.93 (3 H, t, *J* 7) (2 × CH_3); δ_C(75 MHz; $CDCl_3$) 170.0 (C=O), 141.8, 138.3, 133.1, 132.6, 129.1, 129.0, 128.4, 128.3, 127.5, 127.2, 126.4, 125.0, 124.7 (Ar), 72.9 (CHOH), 43.4, 39.1 (2 × CH_2), 13.7 and 13.0 (2 × CH_3); *m*/*z* (CI) 334 (31%, M + H), 318 and 316 (Found: M^+, 333.1724. $C_{22}H_{23}NO_2$ requires *M*, 333.1729).

1-Propylbutylamine 18

A solution of heptan-4-one (2.5 ml, 17.909 mmol), ammonium acetate (13.809 g, 179.087 mmol) and sodium cyanoborohydride (0.790 g, 11.943 mmol) in absolute methanol (54 ml) was stirred for 72 h at 25 °C. Concentrated hydrochloric acid was then added until the pH was <2 (15 ml) and then the methanol was removed under reduced pressure. The residue was taken up in water (50 ml) and extracted with three portions (40 ml) of ether. The aqueous solution was brought to pH > 10 with solid potassium hydroxide, saturated with sodium chloride, and extracted with five portions (30 ml) of ether. The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give pure 1-propylbutylamine as a colourless oil (1.606 g, 78%), bp 142 °C (lit.,[66] 139–140 °C); ν_{max}(film)/cm^{-1} 3366 and 3299; δ_H(200 MHz; $CDCl_3$) 2.65 (1 H, br m, H_2CCH), 1.4–1.1 [8 H, m, $H_2NCH(CH_2CH_2CH_3)_2$], 0.84 (6 H, t, *J* 2, CH_3); δ_C(75 MHz; $CDCl_3$) 50.6, 40.4, 19.3 and 14.2; *m*/*z* (CI) 116 (100%, M + H^+) (Found: M + H^+, 116.1442. $C_7H_{17}N$ requires *M* + H, 116.1439).

Bis(1-propylbutyl)amine 19

5 M HCl–methanol (2.26 ml, 11.261 mmol), heptan-4-one (3.92 ml, 28.152 mmol) and sodium cyanoborohydride (298 mg, 4.504 mmol) were added to a solution of freshly distilled 1-propylbutylamine **18** (1.295 g, 11.261 mmol) in absolute methanol (13 ml). The solution was stirred at 25 °C for 6 days. Concentrated hydrochloric acid was added until the pH was <2 (15 ml) and then the methanol was removed under reduced pressure. The residue was taken up in water (50 ml) and extracted with three portions (40 ml) of ether. The aqueous solution was brought to pH > 10 with solid potassium hydroxide, saturated with sodium chloride, and extracted with five portions (30 ml) of diethyl ether. The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give a mixture of 1-propylbutylamine and the required product. Distillation by Kugelrohr afforded pure *amine* **19** as a colourless oil (1.463 g, 61%), bp 159–160 °C; ν_{max}(film)/cm^{-1} 3370 and 3308; δ_H(300 MHz; $CDCl_3$) 2.46 (2 H, br m, 2 NCH), 1.29 (16 H, m, 4 × $CH_2CH_2CH_3$) and 0.88 (12 H, m, 4 CH_3); δ_C(75 MHz; $CDCl_3$) 54.0, 37.0, 18.7 and 14.3; *m*/*z* (CI) 214 (100%, M + H^+); *m*/*z* (EI) 170 (81%, M − C_3H_7) (Found: M^+, 213.2459. $C_{14}H_{31}N$ requires *M*, 213.2456).

N,*N*-Bis(1-propylbutyl)-1-naphthamide 20

Triethylamine (0.62 ml, 4.46 mmol) was added to a solution of naphthoyl chloride (0.45 ml, 2.972 mmol) in diethyl ether (8 ml) at 0 °C. After 10 min, a solution of bis(1-propylbutyl)amine **19** (633 mg, 2.972 mmol) in ether (8 ml) as added dropwise over 15 min. The reaction vessel was warmed to room temperature and stirred for a further 2 h, then refluxed overnight. The solution was then diluted with water (20 ml) and extracted with three portions (10 ml) of ether. The combined organic phases were washed with two (30 ml) portions of aqueous 1 M hydrochloric acid, two portions (30 ml) of saturated aqueous sodium hydrogen carbonate, water (30 ml) and then dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by column chromatography [10:1 petrol (bp 40–60 °C)–ethyl acetate] to afford the *amide* **20** (760 mg, 70%) as white needles, mp 71–74 °C; R_f [petrol (bp 40–60 °C)–EtOAc (10:1)] 0.26; ν_{max}(film)/cm^{-1} 1624.9 (C=O); δ_H(300 MHz; $CDCl_3$) 7.94–7.76 (3 H, m, Ar*H*), 7.50–7.30 (4 H, m, Ar*H*), 3.20 (1 H, quintet, *J* 6.6, NC*H cis* to C=O), 2.98 (1 H, br m, NC*H trans* to C=O), 2.42 (1 H, m, *trans* $NCHCH_AH_BCH_2CH_3$), 2.15–2.00 (2 H, m, *trans* $NCHCH_2CH_2CH_3$), 1.93 (1 H, m, *trans* $NCHCH_AH_BCH_2CH_3$), 1.55–1.30 (7 H, m, *cis* $NCHCH_2$-CH_2CH_3 × 2, $NCHCH_2CH_2CH_3$, $NCHCH_2CH_AH_BCH_3$), 1.25 (2 H, m, *cis* $NCHCH_2H_AH_BCH_3$, *trans* $NCHCH_2CH_AH_BCH_3$), 1.14 (1 H, m, *cis* $NCHCH_2CH_AH_BCH_3$), 0.97 (1 H, m, *cis* $NCHCH_2H_AH_BCH_3$), 1.01 (3 H, t, *J* 7.3, *trans* CH_3), 0.98 (3 H, t, *J* 7.3, *trans* CH_3), 0.85 (1 H, m, *cis* $NCHCH_2CH_AH_BCH_3$), 0.74 (3 H, t, *J* 6.9, *cis* CH_3) and 0.38 (3 H, t, *J* 7.1, *cis* CH_3); δ_C(75 MHz; $CDCl_3$) 166.5, 131.7, 129.1, 125.4, 123.9, 123.7, 121.8, 121.7, 121.0, 120.3, 118.9, 55.2, 52.0, 32.6, 31.7, 31.1, 30.4, 17.2, 15.6, 10.1, 10.0, 9.5 and 8.9; *m*/*z* (CI) 368 (100%, M + H^+) and 155 [M − N(C_7H_{15})$_2$]; *m*/*z* (EI) 367 (5%, M^+) and 155 (100, [M − N(C_7H_{15})$_2$] (Found: C, 82.04; H, 9.33; N, 3.88%. $C_{25}H_{37}NO$ requires C, 81.7; H, 10.1; N, 3.8%). Assignments in the NMR spectrum were made by COSY.

(Dicyclohexyl)methylamine 21

A solution of dicyclohexyl ketone (13.07 ml, 66.335 mmol), ammonium acetate (51.148 g, 663.340 mmol) and sodium cyanoborohydride (2.926 g, 44.237 mmol) in absolute methanol (200 ml) was stirred for 6 days at 25 °C, then worked up as for 1-propylbutylamine **18** to give pure (*dicyclohexyl*)*methylamine* **21** (8.149 g, 63%) as a colourless oil, bp 210 °C; ν_{max}(film)/cm^{-1} 3387 and 3318; δ_H(300 MHz; $CDCl_3$) 2.22 (1 H, t, *J* 5.5, H_2NCH) and 1.84–0.92 (22 H, m, 2 × C_6H_{11}); δ_C(75 MHz; $CDCl_3$) 60.8, 40.0, 30.7, 27.6, 26.6, 26.5 and 26.3; *m*/*z* (CI) 196 (100%, M + H^+) (Found: M + H^+, 196.2071. $C_{14}H_{31}N$ requires *M* + H, 196.2065).

Lithiation of 20 with *sec*-butyllithium–TMEDA

sec-Butyllithium (0.62 ml of 1.3 M solution in cyclohexane, 0.809 mmol) was added to a stirred solution of TMEDA (0.12 ml, 0.809 mmol) in THF (3.8 ml) under an atmosphere of nitrogen at −78 °C. After stirring for 10 min, a solution of *N*,*N*-bis(1-propylbutyl)-1-naphthamide **20** (243 mg, 0.662 mmol) in THF (1.9 ml) was added. After a further 80 min at −78 °C a solution of DMF (1 ml, excess) in THF (0.9 ml) was added. The mixture was allowed to warm to ambient temperature and water (5 ml) was added. The THF was removed under reduced pressure and the mixture extracted with dichloromethane (3 × 15 ml). The combined organic fractions were washed with brine and then dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by column chromatography [10:1 petrol (bp 40–60 °C)–ethyl acetate] to afford N,N-*bis*(1-*propylbutyl*)-2-(1-*methylpropyl*)-1,2-*dihydronaphthalene*-1-*carboxamide* **23** (115 mg, 41%) as a mixture of diastereoisomers, R_f [petrol (bp 40–60 °C)–EtOAc (10:1)] 0.42; ν_{max}(film)/cm^{-1} 1642; δ_H(300 MHz; $CDCl_3$) (signals for major diastereoisomer) 7.3–7.0 (4 H, m, Ar*H*), 6.55 (1 H, dd, *J* 1.8 and 9.8, ArC*H*=CH), 5.86 (1 H, dd, *J* 9.9, 4.1), 4.04 (1 H, d, *J* 7.8, C*H*CONR$_2$), 3.71 (1 H, quintet, *J* 6.5, NCH), 2.95–2.80 (2 H, m, NCH and ArCH=CHC*H*), 2.24–0.88 {34 H, m, N[CH(C_3H_7)$_2$]$_2$ and C*H*MeC*H*$_2$C*H*$_3$} and 0.84 (3 H, d, *J* 6.7, $CHCH_3Et$); δ_C(75 MHz; $CDCl_3$) (signals for major diastereoisomer) 173.1, 134.0, 133.8, 127.9, 127.7, 127.0, 127.0, 126.9, 126.8, 126.1, 58.6, 56.8, 45.9, 41.9, 38.8, 37.2, 36.7, 36.3, 35.6, 27.6, 21.6, 21.5, 20.7, 20.6, 15.3, 14.4, 14.2 and 12.1; *m*/*z* (CI)

426 (100%, M + H^+); *m*/*z* (EI) 425 (100%, M^+) and 368 (72%, M − C_4H_9) (Found: M + H^+, 425.3656. $C_{29}H_{47}NO$ requires *M* + H, 425.3657).

Also obtained was 2-*formyl*-N,N-*bis*(1-*propylbutyl*)-1-*naphthamide* **24** (116 mg, 44%) as an oil, R_f [petrol bp (40–60 °C)–EtOAc (10:1)] 0.19; ν_{max}(film)/cm^{-1} 1691 and 1615; δ_H(300 MHz; $CDCl_3$) 10.35 (1 H, s, CHO), 8.07–7.47 (6 H, m, ArH), 3.06 (1 H, br m, *cis* NCH), 2.90 (1 H, quintet, *J* 6.1, *trans* NCH), 2.53–2.23 (2 H, m, *cis* NCHC$H_2$$CH_2CH_3$), 2.13–1.87 (2 H, m, *cis* NCHC$H_2$$CH_2CH_3$), 1.59–1.21 (8 H, m, 2 × *cis* NCHCH_2-CH_2CH_3, 2 × *trans* NCHC$H_2$$CH_2CH_3$), 1.17–0.67 (4 H, m, 2 × *trans* NCHCH$_2$CH_2CH_3), 2.05 (3 H, t, *J* 7.3, *cis* CH_3), 0.99 (3 H, t, *J* 7.3, *cis* CH_3), 0.64 (3 H, t, *J* 7.4, *trans* CH_3) and 0.30 (3 H, t, *J* 7.3, *trans* CH_3); δ_C(75 MHz; $CDCl_3$) 190.5, 167.6, 142.1, 136.1, 129.3, 129.2, 129.1, 128.8, 128.3, 127.1, 126.6, 121.9, 60.0, 57.3, 36.9, 36.7, 35.5, 34.9, 21.7, 20.2, 20.0, 14.4, 14.4, 13.5 and 13.0; *m*/*z* (CI) 396 (51%, M + H) and 368 (100, M − OH); *m*/*z* (EI) 395 (4%, M^+) and 155 (100) (Found: M^+, 395.2826. $C_{26}H_{37}NO_2$ requires *M*, 395.2824).

Lithiation of 20 with *sec*-butyllithium, without TMEDA present

In the same way as above, but without TMEDA, amide **20** (240 mg, 0.66 mmol) gave aldehyde **24** (99 mg, 40%) and amide **23** (147 mg, 55%).

(R_a*,1′*R)- and (R_a*,1′*S**)-*N*,*N*-Bis(1-propylbutyl)-2-(1′-hydroxyethyl)-1-naphthamide 25b and 25a (R = Me)**

tert-Butyllithium (0.71 ml of a 1.7 M solution in pentane, 1.203 mmol) was added to a solution of naphthamide **20** (368 mg, 1.003 mmol) in THF (15 ml) under an atmosphere of nitrogen at −78 °C. After 30 min, the solution had turned brown and acetaldehyde (1 ml, excess) was added. After 30 min, the reaction was quenched with saturated aqueous ammonium chloride (5 ml). The mixture was then diluted with water (10 ml) and extracted with dichloromethane (3 × 15 ml) and then dried ($MgSO_4$). Purification by preparative HPLC afforded (R_a*,1′R*)-N,N-*bis*(1-*propylbutyl*)-2-(1′-*hydroxyethyl*)-1-*naphthamide* **25b** (R = Me) (56 mg, 14%) as an oil, R_f [petrol (bp 40–60 °C)–EtOAc (2:1)] 0.57; ν_{max}(film)/cm^{-1} 3391 and 1606; δ_H(300 MHz; $CDCl_3$) 7.9–7.7 (6 H, m, ArH), 5.18 (1 H, q, *J* 6.3, C*H*OH), 3.03 (2 H, quintet, *J* 7.3, 2 × NCH), 2.37 (2 H, m, 2 × NCHC$H_A$$H_B$$CH_2CH_3$), 2.08 (1 H, m, NCH-C$H_A$$H_B$$CH_2CH_3$), 2.00–0.94 (11 H, m), 1.54 (3 H, d, *J* 6.5, COHCH_3), 0.93–0.58 (2 H, m), 1.05 (3 H, t, *J* 7.3, CH_3), 1.01 (3 H, t, *J* 7.3, CH_3), 0.74 (3 H, t, *J* 7.1, CH_3) and 0.36 (3 H, t, *J* 7.3, CH_3); δ_C(75 MHz; $CDCl_3$) 169.4, 139.2, 132.6, 131.6, 129.2, 128.7, 127.9, 126.2, 125.9, 125.5, 122.8, 68.2, 60.0, 56.7, 36.9, 36.9, 36.0, 35.5, 26.2, 21.8, 20.3, 20.2, 14.4, 14.4, 14.0 and 13.2; *m*/*z* (CI) 412 (63%, M + H^+), 396 (100, M − CH_3) and 394 (49, M − OH) (Found: M + H^+, 412.3218. $C_{27}H_{41}NO_2$ requires *M* + H, 412.3215).

Also obtained was (R_a*,1′S*)-N,N-*bis*(1-*propylbutyl*)-2-(1′-*hydroxyethyl*)-1-*naphthamide* **25a** (R = Me) (83 mg, 21%) as an oil, R_f [petrol bp (40–60 °C)–EtOAc (2:1)] 0.50; ν_{max}(film)/cm^{-1} 3426 and 1604; δ_H(300 MHz; $CDCl_3$) 7.92–7.82 (3 H, m, ArH), 7.67 (1 H, d, *J* 8.7, ArH), 7.58–7.47 (2 H, m, ArH), 5.18 (1 H, q, *J* C*H*OH), 3.17–3.00 (2 H, m, NCH), 2.50–2.32 (2 H, m, 2 × NCHC$H_A$$H_B$$CH_2CH_3$), 2.22–2.07 (1 H, m, NCHCH$_A$$H_B$-$CH_2CH_3$), 1.94 (1 H, m, NCHCH$_A$$H_B$$CH_2CH_3$), 1.70 (3 H, d, *J* 6.5, COHCH_3), 1.68–0.80 (11 H, m), 1.09 (3 H, t, *J* 7.3, CH_3), 1.05 (3 H, t, *J* 7.4, CH_3), 0.60 (3 H, t, *J* 7.2, CH_3), 0.65 (1 H, m) and 0.50 (3 H, t, *J* 7.2, CH_3); δ_C(75 MHz; $CDCl_3$) 171.0, 138.7, 133.8, 132.5, 129.3, 129.0, 128.1, 128.0, 126.3, 126.2, 125.0, 122.8, 66.6, 60.3, 57.1, 36.9, 36.8, 36.3, 35.2, 21.8, 21.7, 20.3, 20.2, 19.5, 14.4, 14.4, 13.7 and 13.4; *m*/*z* (CI) 412 (100%, N + H^+) and 394 (94, M − OH); *m*/*z* (EI) 411 (7%, M^+) (Found: M^+, 411.3141. $C_{27}H_{41}NO_2$ requires *M*, 411.3137).

Also obtained was starting material **20** (147 mg, 40%) and NMR of the crude reaction mixture showed the presence of 1-*tert*-butylethanol.

(R_a*,α*R)- and (R_a*,α*S**)-*N*,*N*-Bis(1-propylbutyl)-2-(α-hydroxybenzyl)-1-naphthamide 25b and 25a (R = Ph)**

In the same way, naphthamide **20** (188 mg) gave (R_a*,αR*)-N,N-*bis*(1-*propylbutyl*)-2-(α-*hydroxybenzyl*)-1-*naphthamide* **25b** (R = Ph) (26 mg, 11%), R_f [petrol (bp 40–60 °C)–EtOAc (2:1)] 0.75; ν_{max}(film)/cm^{-1} 3415 and 1606; δ_H(300 MHz; $CDCl_3$) 7.97–7.18 (11 H, m, ArH), 6.21 (1 H, s, C*H*OH), 3.25–3.03 (2 H, m, 2 × NCH), 2.57–2.37 (3 H, m, O*H*, NCHC$H_2$$CH_2CH_3$), 2.15 (1 H, m, NCHC$H_A$$H_B$$CH_2CH_3$), 2.03 (1 H, m, NCHCH$_A$-$H_B$$CH_2CH_3$), 1.73–0.73 (12 H, m), 1.11 (3 H, t, *J* 7.3, CH_3), 1.03 (3 H, t, *J* 7.3, CH_3), 0.84 (3 H, t, *J* 7.1, CH_3) and 0.42 (3 H, t, *J* 7.3, CH_3); δ_C(75 MHz; $CDCl_3$) 169.6, 143.8, 137.0, 132.7, 132.6, 129.3, 128.8, 128.3, 127.9, 127.1, 126.3, 126.2, 125.9, 125.7, 124.1, 72.8, 60.2, 56.9, 37.0, 36.9, 36.2, 35.6, 21.9, 21.8, 20.4, 20.3, 14.5, 14.5, 14.1 and 13.3; *m*/*z* (CI) 474 (100%, M + H^+) and 456 (50, M − OH); *m*/*z* (EI) 473 (5%, M^+) (Found: M^+, 473.3289. $C_{32}H_{43}NO_2$ requires *M*, 473.3294).

Also obtained was (R_a*,αS*)-N,N-*bis*(1-*propylbutyl*)-2-(α-*hydroxybenzyl*)-1-*naphthamide* **25a** (R = Ph) (60 mg, 25%), mp 148–150 °C [petrol bp (40–60 °C)–EtOAc (2:1)] 0.73; ν_{max}(film)/cm^{-1} 3393 and 1601; δ_H(300 MHz; $CDCl_3$) 7.93 (1 H, d, *J* 8.0, ArH), 7.82 (1 H, d, *J* 7.6, ArH), 7.70 (1 H, d, *J* 8.7, ArH), 7.58–7.34 (7 H, m, ArH), 6.99 (1 H, d, *J* 8.7, ArH), 6.20 (1 H, s, CHOH), 4.55 (1 H, br s, OH), 3.22 (1 H, m, NCH), 3.15 (1 H, m, NCH), 2.54–2.30 (2 H, m, NCHC$H_2$$CH_2CH_3$), 2.21 (1 H, m, NCHC$H_A$$H_B$$CH_2CH_3$), 1.91 (1 H, m, NCHCH$_A$$H_B$$CH_2CH_3$), 1.72 (1 H, m, NCHC$H_A$$H_B$$CH_2CH_3$), 1.65–0.6 (11 H, m), 1.09 (3 H, t, *J* 7.3, CH_3), 1.00 (3 H, t, *J* 7.3, CH_3), 0.76 (3 H, t, *J* 7.0, CH_3) and 0.58 (3 H, t, *J* 6.9, CH_3); δ_C(75 MHz; $CDCl_3$); *m*/*z* (CI) 474 (60%, M + H^+) and 456 (100, M − OH); *m*/*z* (EI) 473 (5%, M^+) (Found: M^+, 473.3283. $C_{32}H_{43}NO_2$ requires *M*, 473.3294).

Also obtained was 1-(*tert*-butyl)benzyl alcohol (7 mg) and starting material **20** (88 mg, 47%).

Crystal structure determination of 16b (R = Ph)

Data collection. A colourless tabular crystal of $C_{24}H_{27}NO_2$ having approximate dimensions of 0.20 × 0.30 × 0.45 mm was mounted on a glass fibre. All measurements were made on a Rigaku AFC5R diffractometer with graphite-monochromated Cu-Kα radiation and a 12 kW rotating anode generator.

Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of 20 carefully-centred reflections in the range $50.80 < 2\theta < 59.35°$ corresponded to a monoclinic cell within dimensions: $a = 10.732(8)$ Å, $b = 18.870(4)$ Å, $c = 11.126(3)$ Å, $\beta = 112.62(2)°$, $V = 2080(1)$ Å^3. For $Z = 4$ and $M = 361.48$, $D_c = 1.154$ g cm^{-3}. Based on the systematic absences of: *h*0*l*: $l \neq 2n$, 0*k*0: $k \neq 2n$ and the successful solution and refinement of the structure, the space group was determined to be $P2_1/c$ (#14).

The data were collected at a temperature of 23 ± 1 °C using the ω–2θ scanning technique to a maximum 2θ value of 120.1°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.22° with a take-off angle of 6.0°. Scans of (1.10 + 0.30 tan θ)° were made at a speed of 32.0° min^{-1} (in omega). The weak reflections [$I < 10.0\sigma(I)$] were rescanned (maximum of two rescans) and the counts were accumulated to assure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 0.5 mm and the crystal to detector distance was 400.0 mm.

Data reduction. Of the 3401 reflections which were collected, 3213 were unique ($R_{int} = 0.048$). The intensities of three representative reflections which were measured after every 150 reflections declined by 2.04%. A linear correction factor was applied to the data to account for this phenomenon.

The linear absorption coefficient for Cu-Kα is 5.4 cm^{-1}. An empirical absorption correction, based on azimuthal scans of several reflections, was applied which resulted in transmission factors ranging from 0.94 to 1.00. The data were corrected for

Lorentz and polarization effects. A correction for secondary extinction was applied (coefficient = 0.29391×10^{-7}).

Structure solution and refinement. The structure was solved by direct method.[67] The non-hydrogen atoms were refined anisotropically. The hydrogen atoms except H1, were included in the structure factor calculation in idealized positions (C–H = 0.95 Å), and were assigned isotropic thermal parameters which were 20% greater than the equivalent *B* value of the atom to which they were bonded. H1 was located in a difference Fourier map, and fixed at that position. The short contact between O1 and O2 from another molecule indicates hydrogen bonding interactions. The final cycle of full-matrix least-squares refinement was based on 2133 observed reflections [$I > 3.00\sigma(I)$] and 245 variable parameters and converged (largest parameter shift was <0.01 times its esd) with unweighted agreement factors of: $R = \Sigma||F_o| - |F_c||/\Sigma|F_o| = 0.058$, $R_w = [(\Sigma w(|F_o| - |F_c|)^2/\Sigma w F_o^2)]^{\frac{1}{2}} = 0.076$.

The standard deviation of an observation of unit weight was 2.23. The weighting scheme was based on counting statistics and included a factor ($p = 0.03$) to downweight the intense reflections. Plots of $\Sigma w(|F_o| - |F_c|)^2$ *versus* $|F_o|$, reflection order in data collection, sin θ/λ, and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.17 and -0.15 e$^-$ Å^{-3}, respectively.

Neutral atom scattering factors were taken from Cromer and Waber.[68] Anomalous dispersion effects were included in F_c;[69] the values for $\Delta f'$ and $\Delta f''$ were those of Cromer.[70] All calculations were performed using the TEXSAN crystallographic software package of Molecular Structure Corporation.

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