Atroposelective attack of nucleophiles and electrophiles on 2-acyl-1-naphthamides and their enolates

Jonathan Clayden,* Neil Westlund, Roy L. Beddoes and Madeleine Helliwell

Department of Chemistry, University of Manchester, Oxford Rd., Manchester, UK M13 9PL

Received (in Cambridge, UK) 24th January 2000, Accepted 10th March 2000

Organolithiums, Grignard reagents and borohydride reducing agents attack 2-acyl-1-naphthamides to give tertiary and secondary alcohols with high or complete atroposelectivity. High levels of stereoselectivity can also be obtained in the alkylations of enolates derived from the same ketones, though the low barrier to thermal epimerisation of the product ketones prevents accurate determination of the kinetic stereoselectivity of the alkylation. The direction of attack in both cases is controlled by the perpendicular conformation of the aromatic amide substituent, whose NR_2 group shields one face of the ketone.

Introduction

In 2-substituted and 2,6-disubstituted tertiary benzamides the aromatic ring and the planar, conjugated amide group lie more or less perpendicular.[1] Provided the benzene ring is unsymmetrically substituted, this conformation is chiral, and with a sufficiently large barrier to rotation about the Ar–CO bond the enantiomeric conformers become atropisomers and the compounds are resolvable.[2–5] We recently published our work on the structural features necessary for conformational stability in tertiary aromatic amides, particularly 2-substituted tertiary naphthamides **1**.[6]

The chirality inherent in the Ar–CO bond means that hindered tertiary 1-naphthamides bearing chiral substituents may exist as two diastereoisomers, and we have described the diastereoselective synthesis of 2-(1-hydroxyalkyl)-1-naphthamides by addition of ortholithiated 1-naphthamides to aldehydes.[1,7] The level of diastereoselectivity in these reactions, in which the stereogenic axis and the stereogenic centre are both formed in the same step, reached about 90 : 10.

The use of axial chirality to control relative stereochemistry has received rather less attention than its use (in the form of chiral ligands) to control absolute stereochemistry.[8] In the biaryl series, binaphthyls[9] have been used as chiral auxiliaries to control enolate alkylation,[10–14] conjugate additions to α,β-unsaturated carbonyl compounds,[14–16] nucleophilic attack on aldehydes or ketones,[17–22] intramolecular pinacol reactions,[23–25] cycloadditions,[26] atroposelective formation of a second biaryl axis,[27,28] and desymmetrisation of prochiral anhydrides.[29] Atroposelective reactions of the aromatic rings themselves, generating central chirality from axial chirality, have been observed in the nucleophilic attack of fluoride on an oxidised biphenyl derivative,[30] in the deprotonation/protonation of naphthylfluorenes,[31] and in the oxidations of *N*-naphthylpyrimidine analogues of flavines[32,33] and phenylpyridine analogues of NADH.[34,35]

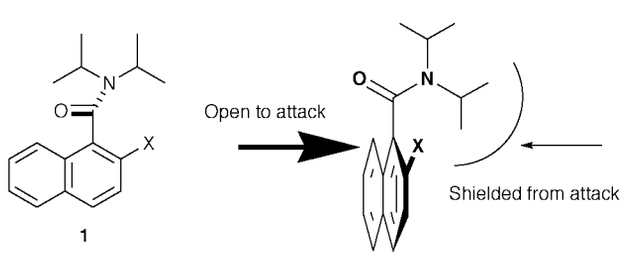


Fig. 1 The directing influence of the amide group.

We reviewed the atroposelective reactions of non-biaryl atropisomers in 1997,[36] and since then there have been further reports that rotational restriction in anilides and maleimides exerts stereocontrol over enolate alkylations,[37–39] aldol reactions,[37] radical additions,[40,41] and cycloadditions.[40–43]

In this paper and the two which follow we describe our studies into the use of a conformationally fixed amide substituent to control the stereochemistry at new chiral centres by influencing the direction in which reagents attack carbonyl groups (and their derivatives) attached to the aromatic ring. We show that the reactions of **1** may generally be explained by a model (Fig. 1) in which the perpendicular arrangement of the amide presents the two faces of the naphthalene ring, and any substituents attached to the ring, with two very different steric environments. One face of the ring is sheltered by the nitrogen's alkyl substituents while the other is much more exposed to attack since the approach of a reagent is hindered only by the carbonyl oxygen atom. This paper will discuss nucleophilic attack on 2-acyl-1-naphthamides[44] and electrophilic attack on their enolates.[45] The next paper[46] will discuss 2-formyl-1-naphthamides and their derivatives, and will highlight the role of metal–carbonyl coordination in their reactions, and the third paper[47] will discuss the stereoselective reactions of 8-acyl-1-naphthamides.

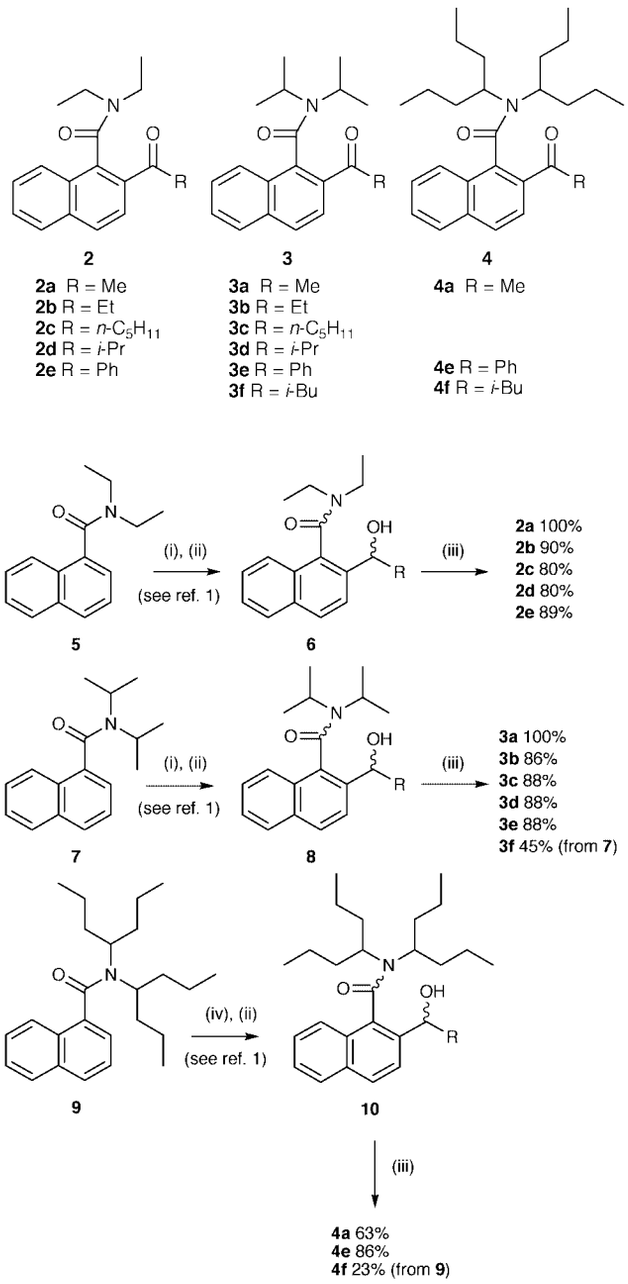
Synthesis of 2-acyl-1-naphthamides

To investigate the ability of the amide to direct attack on substituents attached to the naphthalene ring, we needed a range of ketones **2**–**4**. Each ketone was made by ortholithiation of the parent *N*,*N*-dialkyl-1-naphthamide **5**, **7** or **9** with *s*-BuLi,[48] addition of the organolithium to an aldehyde RCHO,[1] and Jones oxidation of the resulting diastereoisomeric mixtures of alcohols **6**, **8** or **10** (Scheme 1).[49]

Additions of organometallics to 2-acyl-1-naphthamides

Ketones **3b** and **3f** were each treated with methyllithium and with methylmagnesium bromide. The tertiary alcohols **11** and **12** were isolated as single atropisomeric diastereoisomers in excellent yield (Scheme 2). Analytical HPLC of the crude reaction mixtures showed that in each case the diastereoselectivity was >99 : 1. The sense of the selectivity was independent of the metal: both MeLi and MeMgBr gave identical products.

DOI: 10.1039/b000668h



Scheme 1 Synthesis of 2-acylnaphthamides: (i) *s*-BuLi, −78 °C, THF, 30 min; (ii) RCHO, −78 to −20 °C, 30 min; (iii) CrO_3, H_2SO_4, H_2O, acetate, 0–20 °C, 70 min; (iv) *t*-BuLi, −78 °C, THF, 30 min.

The tertiary alcohol **13**, which is diastereoisomeric with **11**, was made by a complementary route from the methyl ketone **3a** and ethylmagnesium bromide. Alcohol **13** was isolated in 96% yield, and analytical HPLC of the crude reaction mixture again showed >99 : 1 diastereoselectivity. The stereochemistry of **13** (and therefore also **11**) was determined by an X-ray crystal structure, shown in Fig. 2, and we assume that **12** is formed with the same sense of diastereoselectivity. Although bond rotation about Ar–CO should interconvert **11** and **13**, the barrier to rotation provided by the fully substituted carbon atom at the 2-position is very high, and **11** and **13** could not be made to interconvert even by heating in toluene at 55 °C for 28 h (more vigorous conditions led to decomposition).

Nucleophilic reductions of 2-acyl-1-naphthamides

We had already made the pairs of diastereoisomeric alcohols **6**, **8** and **10** using the additions to aldehydes summarised in Scheme 1, and had assigned their stereochemistry by a combination of crystallographic and NMR techniques.[1] We were now

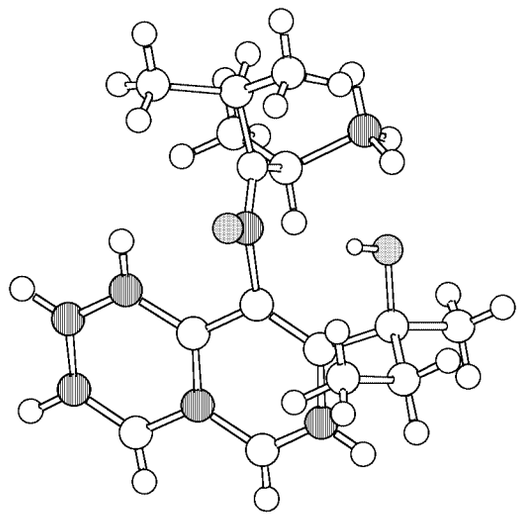
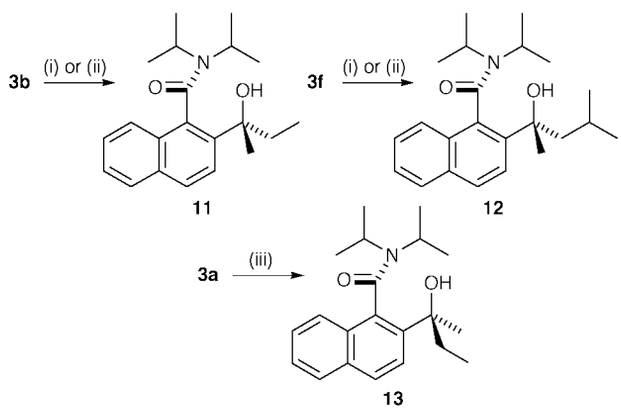


Fig. 2 X-Ray crystal structure of **13**.



Scheme 2 Diastereoselective attack by nucleophiles on 2-acylnaphthamides: (i) MeMgBr, THF, Et_2O, −78 °C; (ii) MeLi, THF, Et_2O, −78 °C; (iii) EtMgBr, THF, Et_2O, −78 °C.

in a position to reduce the ketones **2**–**4** to the corresponding alcohols using some nucleophilic hydride equivalents (Scheme 3). This enabled us to test the effect on the stereoselectivity of varying the size of (a) the nucleophile and (b) the nitrogen's two alkyl substituents. Table 1 shows the result of treating the ketones with each of three reducing agents of increasing steric bulk: $NaBH_4$, $LiEt_3BH$ and $Li(s\text{-}Bu)_3BH$. The crude reaction products were stored at −18 °C and analysed by HPLC to determine product ratios. Yields in every case were essentially quantitative.

The *anti* diastereoisomer is always the major product. In order to clarify the origin of the diastereoselectivity of these and other reactions of ketones **2**–**4** we determined the X-ray crystal structure of ketone **3e** (Fig. 3). The crystal structure shows clearly the perpendicular arrangement of the amide and the ring: the dihedral angle between the amide C=O and the C1–C2 bond of the naphthalene ring is 96°. It also indicates that the C2–C(=O) bond adopts an approximately *s-cis* conformation, maximising conjugation with the ring while avoiding severe steric interactions between Ph and the amide. It is clear that the two faces of the ketone in this conformation are presented with very different steric environments: the amide's bulky NR_2 group blocks one face, leaving the other open to attack by nucleophiles. Exclusive attack from the face opposite the amide's NR_2 group leads to the stereochemistry of **11**–**13**, and preferential attack from this face accounts for the *anti* stereochemistry of the major diastereoisomers of **6**, **8** and **10**. Coordination of the nucleophiles' metal counter-ion to the basic amide carbonyl group may also play a part in controlling stereoselectivity.

Table 1 Stereoselective reduction of ketones **2**, **3** and **4**

Starting materials		**2** + $NaBH_4$	**3** + $NaBH_4$	**2** + $LiEt_3BH$	**3** + $LiEt_3BH$	**4** + $LiEt_3BH$	**3** + $Li(s\text{-}Bu)_3BH$
	R =	*anti*-**6**:*syn*-**6**	*anti*-**8**:*syn*-**8**	*anti*-**6**:*syn*-**6**	*anti*-**8**:*syn*-**8**	*anti*-**10**:*syn*-**10**	*anti*-**8**:*syn*-**8**
a	Me	79:21	82:18 87:13[a]	83:17	93:7	>99:1	86:14
b	Et	86:14	80:20	88:12	93:7	—	89:11
c	$n\text{-}C_5H_{11}$	81:19	86:14	87:13	98:2	—	—
d	*i*-Pr	87:13	89:11	89:11	92:8	—	—
e	Ph	86:14	95:5	97:3	140:1	>99:1	—

[a] Reaction carried out at −40 °C.

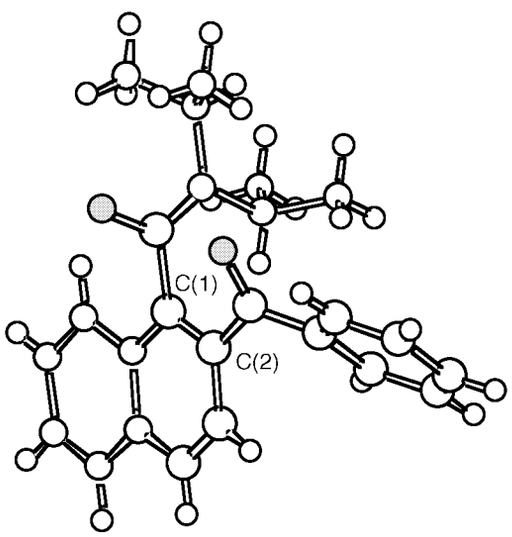
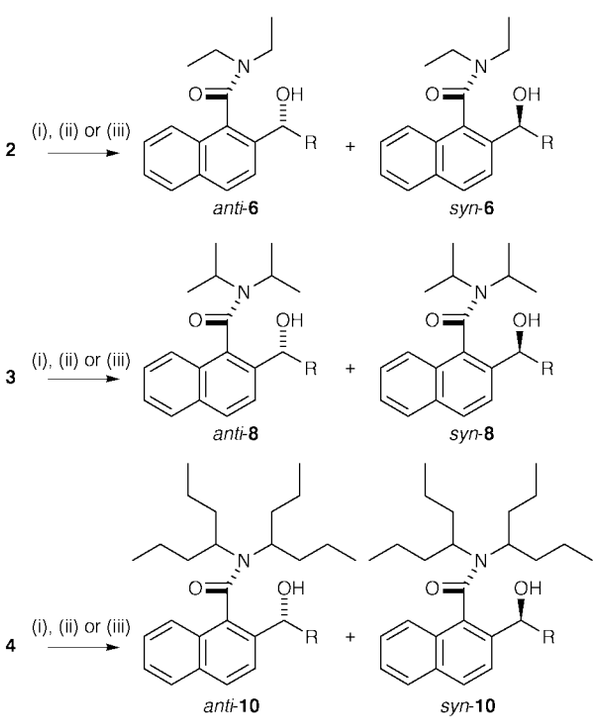


Fig. 3 X-Ray crystal structure of **3e**.



Scheme 3 Stereoselective reduction of ketones **2**–**4**: (i) $NaBH_4$, EtOH, 0 °C; (ii) $LiBHEt_3$, THF, 0 °C; (iii) $Li(s\text{-}Bu)_3BH$, THF, 0 °C.

The difference in selectivity between reductions of ketones **2**–**4** bearing different R groups may be due to fine tuning of the reactive conformation: changing R may affect by a few degrees the angle of attack of the reducing agent relative to the naphthalene ring and the amide substituents. For **2a**–**2d** and **3a**–**3d** there is rather little variation in selectivity between substituents, but the diaryl ketones **3e** and to some extent **2e** are reduced with significantly greater selectivity.

More significant is the change in stereoselectivity on changing *N*-substituents. With $LiBHEt_3$, $N(CHPr_2)_2$ ketones **4** were reduced with complete *anti* selectivity, $N\textit{i}\text{-}Pr_2$ ketones **3** were reduced with >90:10 selectivity, while NEt_2 ketones **2** were reduced with 80:20–90:10 selectivity. The results with the smaller $NaBH_4$ are less consistent. Clearly, in general, larger *N*-substituents block more effectively the more hindered face of the ketone, though in view of the complete selectivity obtained in the reactions of $N\textit{i}\text{-}Pr_2$ ketones **3** with alkyllithium and Grignard reagents it is surprising that as much as 10–20% of the *syn* isomer is formed. The dependence of selectivity on the *N*-substituent could also be a conformational effect, attributable to slight changes in the angle at which the ketone is attacked.

$LiBHEt_3$ was the most stereoselective reducing agent we tried. The less bulky $NaBH_4$ performed less well in almost all cases, and stereoselectivity was not improved by using the even more hindered $LiBH(s\text{-}Bu)_3$. For high stereoselectivity, the choice of reagent is more important than the choice of *N*-substituent, and although $N(CHPr_2)_2$ ketones **4** exhibit the highest levels of selectivity, they are the most inconvenient to make.[1]

Enolate alkylations of 2-acyl-1-naphthamides

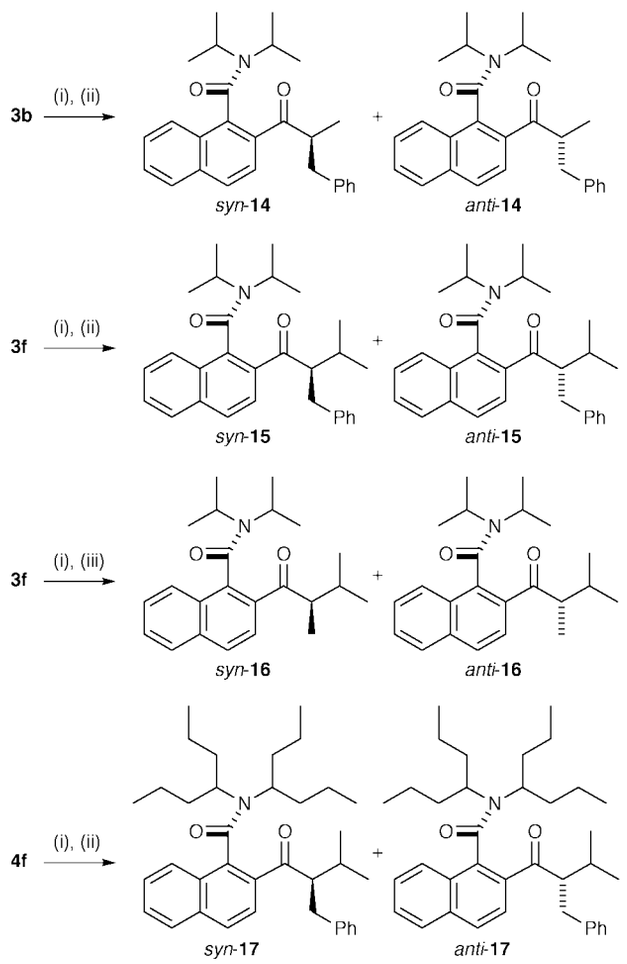
Among the most successful and widely used stereoselective reactions are the alkylations of chiral enolates,[50] and Simpkins has employed the atroposelective alkylation of enolates derived from rotationally restricted anilides in a chiral auxiliary strategy.[37,38,51] We found that the lithium enolate of ketone **3b** was too unreactive to be alkylated by BnBr (Table 2, entry 1), but that the sodium enolates of **3b** and **3f**, made by treating the ketone with NaHMDS at −78 °C, could be alkylated with MeI or BnBr in 1–2 h at room temperature, and gave 82–87% yields of the alkylated ketones **14**–**16** as mixtures of atropisomers (Scheme 4 and Table 2, entries 2–4).

Because of the danger of epimerising the products at this temperature, a point discussed further below, we turned to the even more reactive potassium enolates, formed with KHMDS at −78 °C, to get alkylation at or below 0 °C. The potassium enolate of **3f** was alkylated with MeI at −78 °C, and a cold aqueous work-up of the reaction gave the atropisomeric products in a rather disappointing 67:33 ratio (entry 7). The reaction of the potassium enolate of **3f** with BnBr was too slow to give product at −78 °C, but a 75:25 ratio of benzylated ketones was obtained after alkylation at 0 °C for 30 min, along with 6% of **18**, the product of *O*-alkylation (entry 6). Similarly, the potassium enolate of **4f** gave a 95:5 ratio of diastereoisomers with BnBr at 0 °C (entry 8). The potassium enolate of **3b** reacted with BnBr at room temperature to give a 58:42 mixture of diastereoisomers (entry 5).

Table 2 Stereoselective alkylation of ketone enolates

Entry	Starting ketone	Base	Alkylating[a] agent	Temp./°C	Product	Yield (%)	Ratio[a] *syn*:*anti*	Thermodynamic ratio[b] *syn*:*anti*
1	**3b**	LDA	BnBr	20	—	0	—	—
2	**3b**	NaHMDS	BnBr	20	**14**	85	—	—
3	**3f**	NaHMDS	BnBr	20	**15**	82[c]	—	—
4	**3f**	NaHMDS	MeI	20	**16**	87	—	—
5	**3b**	KHMDS	BnBr	20	**14**	83	58:42	58:42
6	**3f**	KHMDS	BnBr	0	**15**	84[d]	75:25	25:75
7	**3f**	KHMDS	MeI	−78	**16**	71	67:33	48:52
8	**4f**	KHMDS	BnBr	0	**17**	83	95:5	17:83

[a] By NMR. [b] Ratio after standing in ether for several days at 20 °C. [c] With a trace of enol ether **18**. [d] Also isolated 6% of enol ether **18**.



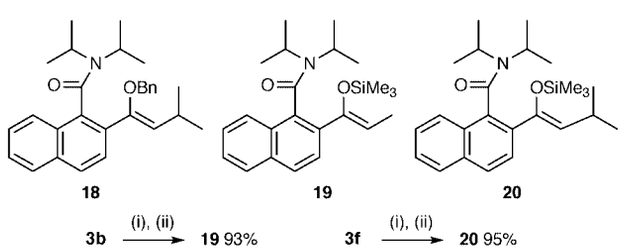
Scheme 4 Alkylation of enolates: (i) base, −78 °C (see Table 2); (ii) BnBr; (iii) MeI.

The poor stereoselectivities observed in most of these reactions may be, at least in part, a consequence of the low barrier to epimerisation (by Ar–CO rotation†) of the products. The atropisomeric diastereoisomers of **14** and **16** were separable by HPLC, but isolation of pure samples of the diastereoisomers was hampered by rapid epimerisation. By cooling the HPLC column and eluent, it was possible to obtain a sample of **16** enriched to 78:22 *syn*:*anti*. Using published methods,[6] we determined a value of 96.8 kJ mol^{-1} for $\Delta G^{\ddagger}_{epim}$, the barrier to epimerisation, of *syn*-**16**. Assuming constancy of $\Delta G^{\ddagger}_{epim}$ with temperature,[6] this corresponds to a half-life for the epimerisation of about 3 h at 20 °C, or 2 days at 0 °C. Rapid bond rotation is typical of atropisomers bearing trigonal blocking substituents.[52] The otherwise comparable secondary alcohols **6** and **8** have half-lives for epimerisation at 20 °C measured in weeks, and the epimerisation of tertiary alcohols **11** and **13** could not be observed at 55 °C (half life at 20 °C >4 years).[6]

It appears therefore that with sodium enolates the rate of product epimerisation approaches the rate of alkylation, and we expect any reaction carried out at 20 °C to give a product ratio significantly affected by epimerisation during the alkylation. To investigate whether the alkylations of the potassium enolates were under purely kinetic control we allowed the product mixtures to stand in solution in ether at 20 °C for 3–7 days (see final column of Table 2). In three cases (entries 6–8) the product mixture attained a thermodynamic equilibrium in which the minor product from the initial reaction mixture constituted the major component. Only the alkylation of **3b** to give **14**, which had been carried out at 20 °C (entry 5), maintained the same ratio of products, which presumably therefore does not represent the kinetic selectivity of the reaction.

We can therefore be sure that the ratios observed directly from the reactions at −78 °C or 0 °C are not purely under thermodynamic control: while some epimerisation may have taken place during reaction or work-up, the major kinetic product is in each case the opposite diastereoisomer from the major thermodynamic product. Nonetheless, only in the alkylation of **4f** at 0 °C to give **17** (entry 8) may we be certain of having isolated close to the kinetic product mixture, which must contain at least 95% *syn*-**17**.

We expect high levels of kinetic stereocontrol only from a geometrically pure intermediate, and silylating the potassium enolates of **3b** and **3f** with Me_3SiCl at −78 °C indeed gave the silyl enol ethers **19** and **20** as single geometrical isomers, which we presume to have *Z* stereochemistry (Scheme 5).



Scheme 5 *O*-Silylation of potassium enolates: (i) KHMDS, −78 °C; (ii) Me_3SiCl, −78 °C.

We were unable to prove unambiguously the stereochemistry of the enolate alkylation products. In an attempt to obtain a crystalline compound for X-ray crystal structure analysis, we reduced with $LiBHEt_3$ the 17:83 mixture of atropisomers obtained from the epimerisation of **17**. Only two products **21** and **22** were formed, and we assume that, like the reductions of **4a** and **4e**, the stereoselectivity of the reaction is controlled entirely by the amide axis, and that each product diastereoisomer arises from a single starting material diastereoisomer

† In the racemic series it is impossible to distinguish between an epimer produced by Ar–CO rotation and one produced by unselective alkylation. In the enantiomerically pure series, of course, the epimers arising in each case would be enantiomeric.

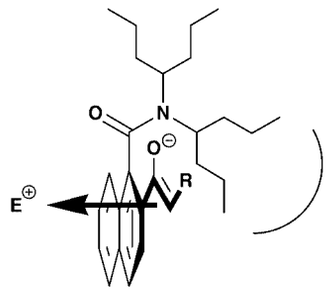
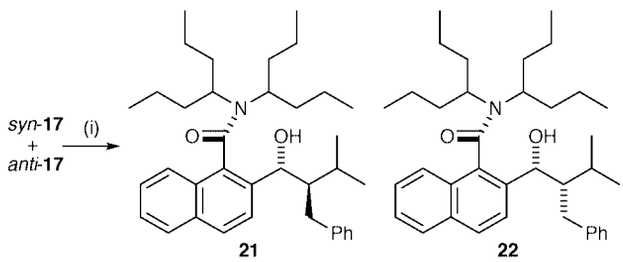


Fig. 4 Stereoselective alkylation of **4f**.



Scheme 6 Reduction of alkylated ketones: (i) $LiBHEt_3$, 0 °C, THF.

(Scheme 6). Unfortunately, while both of the alcohols **21** and **22** were solids, neither gave crystals of sufficiently high quality for X-ray analysis.

We were able to make a tentative assignment of stereochemistry from the fact that the more thermodynamically stable atropisomer is in each case the minor product of enolate alkylation. 350 Conformations of **17** were minimised in a Monte Carlo conformational search (Macromodel 4.5/MM2*):‡ of the 12 lowest energy conformers only one (the fifth most stable, at 9.7 kJ mol^{-1} above the global minimum) had *syn* relative stereochemistry. Similarly, of 100 conformations of **15** found by a Monte Carlo search, the three most stable had *syn* relative stereochemistry, and the most stable *anti* conformer lay 7.6 kJ mol^{-1} above the global minimum. We conclude that *anti*-**17** and *anti*-**15** are more stable than their *syn* epimers, and that the major products of the alkylations have *syn* stereochemistry, presumably arising from attack of the electrophile on the less hindered face of the *cis* enolate in the conformation shown (for **4f**) in Fig. 4. Rationalising the degree of stereoselectivity is impossible because it is not clear how much the lower selectivities obtained with **3** reflect a lower level of kinetic stereocontrol and how much simply a greater propensity to epimerise at the reaction temperature.

Ketone **4f** is the only compound in which the amide axis is demonstrably able to control enolate alkylation. The $N(CHPr_2)_2$ amides **4** illustrate well the power of a suitably substituted amide axis to control stereoselectivity: they can be both alkylated and reduced highly stereoselectively; the enolate alkylation product can usefully be thermally epimerised to give the other diastereoisomer, and each of these two diastereoisomers can be reduced to a single alcohol. However, the low yields in the synthesis of **9** and **4**, and the lack of crystallinity in the derivatives of **5**, have meant that we have used **7** and its derivatives for most subsequent work.

Experimental

Flash chromatography refers to chromatography carried out on silica by the method of Still, Kahn and Mitra.[54] Analytical HPLC was carried out on a Waters Z Module (10 cm by 8 mm, packed SiO_2 stationary phase) at a pressure of 200 lb in^{-2} 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 a pressure of 0.15 kPa 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. Ether refers to diethyl ether; petrol refers to petroleum ether (bp 40–60 °C). *J* values are in Hz. Barriers to racemisation or epimerisation of **3b**, **6a**, **6e**, **8a**, **8b**, **8e**, **13** and **16** have been published elsewhere.[6]

2-Acetyl-*N*,*N*-diethyl-1-naphthamide 2a

A stock solution of oxidising agent was prepared by dissolving CrO_3 (2.5 g) in 20% sulfuric acid. The mixture of diastereoisomeric alcohols **6a**[1] (219 mg, 0.81 mmol) was dissolved in acetone (8 ml) and the solution was cooled to 0 °C. The CrO_3 solution (0.8 ml) was added, and the orange mixture was stirred for 40 min at 0 °C and 30 min at room temperature. The reaction mixture was poured into saturated $NaHCO_3$ solution (50 ml) and extracted with EtOAc (20 ml × 4). The combined organic extracts were washed with water (50 ml), dried ($MgSO_4$) and concentrated under reduced pressure to afford the *ketone* **2a** (218 mg, 100%), as a white solid which was used without further purification. R_f (EtOAc) 0.45; ν_{max}(film)/cm^{-1} 3015, 1687, 1619; δ_H(200 MHz, $CDCl_3$) 8.0–7.8 (4 H, m, ArH), 7.7–7.5 (2 H, m, ArH), 3.85 (1 H, dq, *J* 14 and 7, NCH_AH_BMe), 3.65 (1 H, dq, *J* 14 and 7, NCH_AH_BMe), 3.02 (2 H, q, *J* 7, NCH_2Me), 2.69 (3 H, s, MeCO), 1.44 (3 H, t, *J* 7, NCH_2Me) and 0.90 (3 H, t, *J* 7, NCH_2Me); δ_C(75 MHz, $CDCl_3$) 199.0, 169.5, 136.5, 135.1, 131.1, 129.7, 128.7, 128.4, 128.0, 127.6, 126.9, 124.9, 42.8, 38.7, 28.6, 13.3 and 12.3; *m*/*z* (CI) 270 (100%, $M + H^+$) and 197 (73%, $M - NEt_2$) (Found: M^+, 269.1412. $C_{17}H_{19}NO_2$ requires *M*, 269.1416).

N,*N*-Diethyl-2-propanoyl-1-naphthamide 2b

In the same way, the alcohols **6b**[1] (390 mg, 1.37 mmol) gave the *ketone* **2b** (348 mg, 90%) as a white solid which was used without further purification. ν_{max}(film)/cm^{-1} 2990, 1689, 1619; δ_H(200 MHz, $CDCl_3$) 8.0–7.8 (4 H, m, ArH), 7.6–7.4 (2 H, m, ArH), 3.75 (2 H, ABX_3 m, NCH_2Me), 3.15–2.85 (4 H, m, NCH_2Me and $MeCH_2CO$), 1.42 (3 H, t, *J* 7, NCH_2Me), 1.20 (3 H, t, *J* 7, $MeCH_2CO$) and 0.88 (3 H, t, *J* 7, NCH_2Me); δ_C(75 MHz, $CDCl_3$) 202.0, 169.6, 136.2, 134.9, 131.5, 129.7, 128.6, 128.2, 128.0, 127.5, 127.2, 126.7, 124.3, 43.0, 38.8, 34.0, 13.3, 12.5 and 8.2; *m*/*z* (CI) 284 (90%, $M + H^+$), 211 (80%, $M - NEt_2$) and 72 (100%, NEt_2^+) (Found: M^+, 283.1566. $C_{18}H_{21}NO_2$ requires *M*, 283.1572).

N,*N*-Diethyl-2-hexanoyl-1-naphthamide 2c

In the same way, the alcohols **6c**[1] (140 mg, 0.43 mmol) gave a crude product which was purified by flash chromatography (eluting with 2 : 1 petrol–EtOAc) the *ketone* **2c** (112 mg, 80%) as a white solid. R_f (2 : 1 petrol–EtOAc) 0.36; ν_{max}(film)/cm^{-1} 3013, 2968, 1688, 1620; δ_H(200 MHz, $CDCl_3$) 8.0–7.8 (4 H, m, ArH), 7.6–7.5 (2 H, m, ArH), 3.75 (2 H, ABX_3 m, NCH_2Me), 3.0 (4 H, m, NCH_2Me and CH_2CO), 1.72 (2 H, m, CH_2CH_2CO), 1.40 (3 H, t, *J* 7, NCH_2Me), 1.35 (4 H, m, $MeCH_2CH_2$) and 0.92 (6 H, t, *J* 7, NCH_2Me and $MeCH_2CH_2$); δ_C(75 MHz, $CDCl_3$) 201.8, 169.5, 136.2, 134.9, 131.8, 129.7, 128.6, 128.2, 128.0, 127.5, 126.7, 124.4, 43.0, 40.8, 38.7, 31.5, 24.0, 22.5, 14.0, 13.3 and 12.5; *m*/*z* (CI) 326 (100%, $M + H^+$) and 253 (65%, $M - NEt_2$) (Found: M^+, 325.2045. $C_{21}H_{27}NO_2$ requires *M*, 325.2042).

N,*N*-Diethyl-2-(2-methylpropanoyl)-1-naphthamide 2d

In the same way, the alcohols **6d**[1] (498 mg, 1.66 mmol) gave the *ketone* **2d** (399 mg, 80%) as a waxy solid. R_f (1 : 1 petrol–EtOAc)

‡ The Monte Carlo search was carried out using the MM2* forcefield in Macromodel 4.5,[53] using a G3 Macintosh with X-windows emulation of a Silicon Graphics workstation. Seven (**15**) or fifteen (**17**) rotatable bonds were selected, and the Polak–Ribière method was used to minimise the energy of each conformation.

0.47; ν_{max}(film)/cm^{-1} 3010, 2978, 1688, 1619; δ_H(200 MHz, $CDCl_3$) 8.0–7.8 (3 H, m, ArH), 7.75 (1 H, d, *J* 9, ArH), 7.6–7.5 (2 H, m, ArH), 3.72 (2 H, ABX_3 m, $J_{AX} = J_{BX} = 7$, NC*H*$_2$Me), 3.49 (1 H, septet, *J* 7, C*H*Me$_2$), 3.04 (2 H, q, *J* 7, NC*H*$_2$Me), 1.40 (3 H, t, *J* 7, NCH$_2$*Me*), 1.23 (3 H, d, *J* 7, CH*Me*$_A$Me$_B$), 1.18 (3 H, d, *J* 7, CHMe$_A$*Me*$_B$) and 0.91 (3 H, t, *J* 7, NCH$_2$*Me*); δ_C(75 MHz, $CDCl_3$) 206.3, 169.4, 136.3, 134.7, 132.0, 130.0, 128.5, 128.05, 128.0, 127.5, 126.6, 124.1, 43.1, 38.8, 37.7, 18.8, 18.6, 13.4 and 12.6; *m*/*z* (CI) 298 (80%, M + H$^+$) and 225 (100%, M − NEt$_2$) (Found: M$^+$, 297.1723. $C_{19}H_{23}NO_2$ requires *M*, 297.1729).

2-Benzoyl-*N*,*N*-diethyl-1-naphthamide 2e

In the same way, the alcohols **6e**[1] (525 mg, 1.4 mmol) gave the *ketone* **2e** (435 mg, 83%) as a gum. R_f (4 : 1 petrol–EtOAc) 0.25; ν_{max}(film)/cm^{-1} 3007, 1661, 1620; δ_H(200 MHz, $CDCl_3$) 8.0–7.4 (11 H, m, ArH), 3.76 (1 H, dq, *J* 14 and 7, NC*H*$_A$H$_B$Me), 3.48 (1 H, dq, *J* 14 and 7, NCH$_A$*H*$_B$Me), 3.18 (2 H, q, *J* 7, NC*H*$_2$-Me), 1.26 (3 H, t, *J* 7, NCH$_2$*Me*), 1.23 (3 H, d, *J* 7, CH*Me*$_A$Me$_B$) and 0.98 (3 H, t, *J* 7, NCH$_2$*Me*); δ_C(75 MHz, $CDCl_3$) 197.0, 168.5, 137.3, 136.3, 134.4, 133.1, 130.4, 129.6, 128.3, 128.2, 127.9, 127.8, 127.6, 127.2, 126.3, 125.6, 43.4, 38.7, 13.5 and 12.5; *m*/*z* (CI) 332 (40%, M + H$^+$) and 259 (100%, M − NEt$_2$) (Found: M$^+$, 331.1568. $C_{19}H_{23}NO_2$ requires *M*, 331.1572).

2-Acetyl-*N*,*N*-diisopropyl-1-naphthamide 3a

In the same way, the alcohols **8a**[1] (386 mg, 1.29 mmol) gave the *ketone* **3a** (383 mg, 100%). The crude product was recrystallised from ethanol to afford yellow prisms. Mp 184–186 °C (EtOH), λ_{max}/nm (ε_{max}) (CH_2Cl_2) 252 (57654), 294 (9168), 338 (2847); ν_{max}(film)/cm^{-1} 2976, 2935, 2904, 2875, 1690, 1621; δ_H(300 MHz, $CDCl_3$) 8.06 (1 H, d, *J* 8, ArH), 7.88 (3 H, m, ArH), 7.60 (2 H, m, ArH), 3.66 (1 H, septet, *J* 6.5, NCH), 3.39 (1 H, septet, *J* 6.5, NCH), 2.71 (3 H, s, $COCH_3$), 1.81 (6 H, d, *J* 6.5, 2 × NCHC*H*$_3$), 1.13 (3 H, d, *J* 6.5, NCHC*H*$_3$) and 0.96 (3 H, d, *J* 6.5, NCHC*H*$_3$); δ_C(75 MHz, $CDCl_3$) 198.8, 168.9, 137.2, 135.1, 130.4, 129.6, 128.3, 128.1, 127.9, 127.2, 126.8, 125.0, 51.3, 46.1, 28.7, 20.8, 20.7, 20.0 and 19.7; *m*/*z* (CI) 298 (100%, M + H$^+$) (Found: M + H$^+$, 298.1801. $C_{19}H_{23}NO_2$ requires *M* + H, 298.1807).

N,*N*-Diisopropyl-2-propanoyl-1-naphthamide 3b

In the same way, the alcohols **8b**[1] (260 mg, 0.83 mmol) gave a crude product which was recrystallised from ethanol to afford the *ketone* **3b** (222 mg, 86%) as pale yellow needles. Mp 170–174 °C; ν_{max}(film)/cm^{-1} 2976, 2935, 2904, 2875, 1690, 1621; δ_H(300 MHz, $CDCl_3$) 7.93 (1 H, m, ArH), 7.73 (3 H, m, ArH), 7.45 (2 H, m, ArH), 3.52 (1 H, septet, *J* 6.5, NCH), 3.28 (1 H, septet, *J* 6.5, NCH), 2.95 (2 H, m, C*H*$_2$CH$_3$), 1.68 (6 H, d, *J* 6.5, 2 × NCHC*H*$_3$), 1.13 (3 H, t, *J* 7.0, CH$_2$C*H*$_3$), 1.00 (3 H, d, *J* 6.5, NCHC*H*$_3$) and 0.83 (3 H, d, *J* 6.5, NCHC*H*$_3$); δ_C(75 MHz, $CDCl_3$) 201.8, 168.9, 136.7, 134.9, 130.9, 129.6, 128.1, 128.0, 127.9, 127.1, 126.7, 124.4, 51.3, 46.0, 34.0, 20.8, 20.7, 19.9, 19.8 and 8.2; *m*/*z* (CI) 312 (67%, M + H$^+$) and 180 (100%) (Found: M$^+$, 311.1881. $C_{20}H_{25}NO_2$ requires *M*, 311.1885).

N,*N*-Diisopropyl-2-hexanoyl-1-naphthamide 3c

In the same way, the alcohols **8c**[1] (602 mg, 1.76 mmol) gave the *ketone* **3c** (527 mg, 88%) as a white solid. R_f (2 : 1 petrol–EtOAc) 0.47; ν_{max}(film)/cm^{-1} 3016, 2976, 1686, 1620; δ_H(200 MHz, $CDCl_3$) 8.05 (1 H, m, ArH), 7.8 (3 H, m, ArH), 7.6–7.5 (2 H, m, ArH), 3.60 (1 H, septet, NC*H*Me$_2$), 3.36 (1 H, septet, NC*H*Me$_2$), 2.98 (2 H, ABXY m, C*H*$_2$CO), 1.75 (6 H, d, *J* 7, NCH*Me*$_2$), 1.73 (2 H, m, C*H*$_2$CH$_2$CO), 1.35 (4 H, m, C*H*$_2$C*H*$_2$Me), 1.10 (3 H, d, *J* 7, NCH*Me*$_A$Me$_B$), 0.91 (3 H, d, *J* 7, NCHMe$_A$*Me*$_B$) and 0.88 (3 H, t, CH$_2$*Me*); δ_C(75 MHz, $CDCl_3$) 202.0, 168.9, 136.9, 135.0, 131.4, 129.8, 128.1, 128.05, 128.0, 127.2, 126.8, 124.5, 51.4, 46.2, 41.1, 31.5, 24.1, 22.5, 20.9, 20.8, 20.1, 20.0 and 14.0; *m*/*z* (CI) 354 (70%, M + H$^+$), 253 (75%) and 100 (100%) (Found: M$^+$, 353.2348. $C_{23}H_{31}NO_2$ requires M, 325.2355).

N,*N*-Diisopropyl-2-(2-methylpropanoyl)-1-naphthamide 3d

In the same way, the alcohols **8d**[1] (750 mg, 2.25 mmol) gave the *ketone* **3d** (663 mg, 88%) as a white solid. ν_{max}(film)/cm^{-1} 3016, 2978, 1688, 1621; δ_H(200 MHz, $CDCl_3$) 8.0 (1 H, m, ArH), 7.85 (2 H, m, ArH), 7.72 (1 H, d, *J* 9, ArH), 7.6–7.5 (2 H, m, ArH), 3.59 (1 H, septet, *J* 7), 3.51 (1 H, septet, *J* 7), 3.39 (1 H, septet, *J* 7, CHMe$_2$ × 3), 1.76 (3 H, d, *J* 7, NCH*Me*$_A$Me$_B$), 1.72 (3 H, d, *J* 7, NCHMe$_A$*Me*$_B$), 1.23 (3 H, d, *J* 7, COCH*Me*$_A$Me$_B$), 1.19 (3 H, d, *J* 7, COCHMe$_A$*Me*$_B$), 1.13 (3 H, d, *J* 7, NCH-*Me*$_A$Me$_B$) and 0.93 (3 H, d, *J* 7, NCHMe$_A$*Me*$_B$); δ_C(75 MHz, $CDCl_3$) 206.4, 168.8, 136.7, 134.7, 131.7, 129.8, 128.0, 127.95, 127.9, 127.2, 126.6, 124.3, 51.3, 46.1, 37.9, 20.9, 20.7, 20.0, 19.9, 18.7 and 18.6; *m*/*z* (CI) 328 (60%, M + H$^+$), 225 (90%) and 100 (100%) (Found: M$^+$, 325.2034. $C_{19}H_{23}NO_2$ requires *M*, 325.2042).

2-Benzoyl-*N*,*N*-diethyl-1-naphthamide 3e

In the same way, the alcohols **8e**[1] (94 mg, 0.25 mmol) gave the *ketone* **3e** (82 mg, 88%) as a solid. R_f (4 : 1 petrol–EtOAc) 0.22; ν_{max}(film)/cm^{-1} 3016, 2978, 1664, 1625; δ_H(200 MHz, $CDCl_3$) 8.05–7.4 (11 H, m, ArH), 3.63 (1 H, septet, *J* 7, NC*H*Me$_2$), 3.53 (1 H, septet, *J* 7, NC*H*Me$_2$), 1.69 (3 H, d, *J* 7, NCH*Me*$_A$Me$_B$), 1.42 (3 H, d, *J* 7, NCHMe$_A$*Me*$_B$), 1.20 (3 H, d, *J* 7, NCH-*Me*$_A$Me$_B$) and 0.98 (3 H, d, *J* 7, NCHMe$_A$*Me*$_B$); δ_C(75 MHz, $CDCl_3$) 197.1, 168.0, 137.6, 136.9, 134.4, 133.0, 132.6, 130.6, 128.6, 128.2, 127.8, 127.4, 127.3, 126.4, 125.8, 51.5, 46.2, 21.0, 20.6, 20.0 and 19.8; *m*/*z* (CI) 360 (30%, M + H$^+$), 259 (100%) and 100 (85%) (Found: M$^+$, 359.1876. $C_{24}H_{25}NO_2$ requires *M*, 359.1885).

N,*N*-Diisopropyl-2-(3′-methylbutanoyl)-1-naphthamide 3f

Following our previously published method[1] for the synthesis of alcohols **8**, *s*-butyllithium (27.0 ml of a 1.3 M solution in hexanes, 35.2 mmol) and, 30 min later, isovaleraldehyde (6.0 ml, 5.6 mmol) were added to a solution of naphthamide **7** (6.900 g, 27.06 mmol) in THF (150 ml) at −78 °C. After 30 min the mixture was warmed to −20 °C, quenched with saturated aqueous ammonium chloride solution (30 ml) and worked up as described to yield the crude *alcohols* **8f** as an oil. Without further purification, the crude alcohols **8f** were oxidised by the method used for **2a** to yield a crude product which was recrystallised from ethanol to give the *ketone* **3f** (4.165 g, 45%) as white prisms. Mp 135–136 °C (EtOH); ν_{max}(film)/cm^{-1} 3062, 2971, 2958, 2933, 2871, 1688, 1629; δ_H(300 MHz, $CDCl_3$) 8.1–7.5 (6 H, m, ArH), 3.66 (1 H, septet, *J* 7, NCH), 3.43 (1 H, septet, *J* 7, NCH), 2.92 (2 H, d, *J* 7, CH$_2$), 2.33 (1 H, nonet, *J* 7, CH$_2$C*H*), 1.80 (3 H, d, *J* 7, NCHC*H*$_3$), 1.78 (3 H, d, *J* 7, NCHC*H*$_3$), 1.17 (3 H, d, *J* 7, NCHC*H*$_3$), 1.04 (3 H, d, *J* 6.5, CH$_2$CHC*H*$_3$), 1.03 (3 H, d, *J* 6.5, CH$_2$CHC*H*$_3$) and 0.96 (3 H, d, *J* 6.5, NCHC*H*$_3$); δ_C(75 MHz, $CDCl_3$) 201.7, 168.8, 136.8, 134.8, 131.6, 129.6, 128.0, 127.9, 127.1, 126.7, 124.4, 51.3, 49.8, 46.1, 25.2, 22.7, 22.6, 20.7, 20.6, 19.9 and 19.8; *m*/*z* (CI) 340 (100%, M + H$^+$); *m*/*z* (EI) 339 (3%, M$^+$) and 49 (100%) (Found: C, 77.85; H, 8.74; N, 4.15%. $C_{22}H_{29}NO_2$ requires C, 77.9; H, 8.6; N, 4.1%).

2-Acetyl-*N*,*N*-bis(4-heptyl)-1-naphthamide 4a

By the method used for **2a**, the alcohols **10a**[1] gave, after purification by flash chromatography (2 : 1 petrol–EtOAc), the *ketone* **4a** (99 mg, 63%) as a colourless oil. R_f (2 : 1 petrol–EtOAc) 0.40; ν_{max}(film)/cm^{-1} 2958, 2930, 2870, 1680, 1624; δ_H(300 MHz, $CDCl_3$) 8.09 (1 H, m, ArH), 7.84 (3 H, m, ArH), 7.55 (2 H, m, ArH), 3.00 (1 H, m, NCH), 2.80 (1 H, m, NCH), 2.68 (3 H, s, $COCH_3$), 2.47–2.03 (4 H, m, 2 × NCHC*H*$_2$CH$_2$CH$_3$), 1.69–0.54

(12 H, m, 2 × NCHCH_2CH$_2$CH$_3$ and 4 × NCHCH$_2$CH_2CH$_3$), 1.04 (3 H, t, *J* 7, NCHCH$_2$CH$_2$CH_3), 1.03 (3 H, t, *J* 7, NCHCH$_2$CH$_2$CH_3), 0.69 (3 H, t, *J* 7, NCHCH$_2$CH$_2$CH_3) and 0.37 (3 H, t, *J* 7, NCHCH$_2$CH$_2$CH_3); δ_C(75 MHz, CDCl$_3$) 198.3, 169.4, 136.9, 135.1, 130.4, 129.9, 128.2, 127.7, 127.7, 126.8, 124.9, 59.8, 56.9, 36.9, 35.9, 35.4, 28.8, 21.9, 21.7, 20.4, 20.0, 14.4, 14.4, 13.8 and 13.0; *m*/*z* (CI) 410 (100%, M + H$^+$); *m*/*z* (EI) 409 (13%, M$^+$) and 197 (100%) (Found: M$^+$, 409.2974. $C_{27}H_{39}NO_2$ requires *M*, 409.2981).

2-Benzoyl-*N*,*N*-bis(4-heptyl)-1-naphthamide 4e

In the same way, the alcohols **10e** (101 mg, 0.21 mmol) gave a crude product which was purified by flash chromatography (3 : 1 petrol–EtOAc) to yield the *ketone* **4e** (87 mg, 86%) as a waxy white solid. ν_{max}(film)/cm^{-1} 2958, 2932, 2871, 1662, 1627; δ_H(300 MHz, CDCl$_3$) 8.09 (1 H, m, ArH), 7.88 (4 H, m, ArH), 7.57 (4 H, m, ArH), 7.44 (2 H, m, ArH), 3.70 (1 H, m, NCH), 2.87 (1 H, m, NCH), 2.29 (1 H, m, NCHCH_AH$_B$CH$_2$CH$_3$), 2.03–1.77 (2 H, m, NCHCH_2CH$_2$CH$_3$), 1.61–0.57 (13 H, m, NCHCH_AH$_B$CH$_2$CH$_3$, 2 × NCHCH_2CH$_2$CH$_3$, 4 × NCHCH$_2$-CH_2CH$_3$), 0.99 (3 H, t, *J* 7.1, CH$_3$), 0.83 (3 H, t, *J* 7.3, CH$_3$), 0.73 (3 H, t, *J* 7.3, CH$_3$) and 0.47 (3 H, t, *J* 7.4, CH$_3$); δ_C(75 MHz, CDCl$_3$) 196.6, 168.0, 137.0, 135.4, 134.5, 133.1, 132.2, 130.8, 129.9, 128.1, 127.9, 127.9, 127.7, 127.2, 126.9, 125.7, 60.2, 57.0, 36.9, 36.5, 35.7, 34.8, 21.7, 21.6, 20.5, 20.1, 14.4, 14.4, 14.0 and 13.2; *m*/*z* (CI) 472 (100%, M + H$^+$); *m*/*z* (EI) 471 (4%, M$^+$) and 84 (100%) (Found: M$^+$, 471.3149. $C_{32}H_{41}NO_2$ requires *M*, 471.3137).

N,*N*-Bis(4-heptyl)-2-(3′-methylbutanoyl)-1-naphthamide 4f

tert-Butyllithium (1.06 ml of a 1.7 M solution in pentane, 1.80 mmol) was added to a solution of naphthamide **9**[1] (602 mg, 1.64 mmol) in THF (27 ml) at −78 °C under an atmosphere of nitrogen and the mixture was stirred at −78 °C for 2 hours. The resulting brown solution was treated with isovaleraldehyde (0.57 ml, 4.92 mmol), stirred for 60 minutes, warmed to ambient temperature and quenched with saturated aqueous ammonium chloride (10 ml). The THF was removed under reduced pressure and the resulting aqueous suspension was extracted with dichloromethane (4 × 15 ml). The combined organic extracts were dried (MgSO$_4$), filtered and concentrated under reduced pressure to afford the crude alcohols **10f**. Without further purification, the alcohols **10f** were oxidised by the method used for **2a**. Purification by flash chromatography on silica gel (10 : 1 petrol–EtOAc) afforded the *ketone* **4f** (167 mg, 23%) as a white solid. Mp 124–125 °C (EtOAc); R_f 0.24 (5 : 1 petrol–EtOAc); ν_{max}(film)/cm^{-1} 2957, 2932, 2870, 1687, 1624; δ_H(300 MHz, CDCl$_3$) 7.98 (1 H, m, ArH), 7.9–7.8 (3 H, m, ArH), 7.6–7.5 (2 H, m, ArH), 3.00 (1 H, br m, NCH), 2.90 (2 H, d, *J* 6.5, COCH$_2$), 2.82 (1 H, br m, NCH), 2.5–2.0 (5 H, m, 2 × NCH-CH_2CH$_2$CH$_3$ and CH(CH$_3$)$_2$), 1.72–1.14 (10 H, m, 2 × NCH-CH_2CH$_2$CH$_3$ and 3 × NCHCH$_2$CH_2CH$_3$), 1.10–0.97 (12 H, m, 2 × NCHCH$_2$CH$_2$CH_3 and CH(CH_3)$_2$), 0.71 (3 H, t, *J* 7, NCH(CH$_2$)$_2$CH_3), 0.67 (2 H, m, NCHCH$_2$CH_2CH$_3$) and 0.22 (3 H, t, *J* 7.3, NCH(CH$_2$)$_2$CH_3); δ_C(75 MHz, CDCl$_3$) 201.1, 169.4, 136.3, 134.8, 131.6, 129.9, 128.1, 128.0, 127.7, 127.5, 126.7, 124.4, 59.8, 57.0, 50.0, 36.8, 36.0, 35.9, 25.0, 22.7, 22.7, 21.9, 21.7, 20.5, 20.1, 14.4, 13.8 and 13.1; *m*/*z* (CI) 452 (100%, M + H$^+$) (Found: M$^+$, 451.3453. $C_{30}H_{45}NO_2$ requires *M*, 451.3450).

(*R*$_a$*,1′*R**)-*N*,*N*-Diisopropyl-2-(1′-hydroxy-1′-methylpropyl)-1-naphthamide 11

Methylmagnesium bromide (0.08 ml, 0.24 mmol; 3 M in diethyl ether) was added dropwise to a solution of ketone **3b** (63 mg, 0.20 mmol) in THF (6 ml) at −78 °C under an atmosphere of nitrogen. The mixture was stirred for 3 hours. Saturated ammonium chloride solution (5 ml) was added, and the mixture was warmed to ambient temperature. The THF was removed under reduced pressure at ambient temperature and the aqueous residue was extracted with dichloromethane (4 × 10 ml). The combined organic fractions were washed with brine (30 ml), dried (MgSO$_4$), filtered and concentrated under reduced pressure at ambient temperature to afford the crude product as a brown solid. Analytical HPLC of the crude product indicated the presence of no more than 1% **13**. Flash chromatography (4 : 1 petrol–EtOAc) afforded the *alcohol* **11** (57 mg, 86%) as a white solid. t_R 7.9 min (4 : 1 hexane–EtOAc); R_f 0.61 (2 : 1 petrol–EtOAc); mp 146–148 °C (EtOAc); ν_{max}(film)/cm^{-1} 3387–3424, 1609; δ_H(300 MHz, CDCl$_3$) 8.0–7.3 (6 H, m, ArH), 3.6 (2 H, m, 2 × NCH), 2.14 (1 H, dq, *J* 14 and 7.5, CH_AH$_B$CH$_3$), 1.93 (1 H, dq, *J* 14 and 7.5, CH$_A$$H_BCH_3$), 1.81 (3 H, d, *J* 7, NCHCH_3), 1.68 (3 H, d, *J* 7, NCHCH_3), 1.64 (3 H, s, C(OH)CH_3), 1.19 (3 H, d, *J* 6.5, NCHCH_3), 1.00 (3 H, d, *J* 6.5, NCHCH_3) and 0.97 (3 H, t, *J* 7.5, CH$_2$CH_3); δ_C(75 MHz, CDCl$_3$) 172.7, 141.7, 131.9, 131.9, 130.1, 127.9, 127.6, 126.3, 125.8, 125.0, 124.9, 76.9, 51.4, 46.0, 35.3, 32.5, 20.3, 20.2, 19.75, 19.7 and 8.4; *m*/*z* (CI) 328 (97%, M + H$^+$) and 310 (100%, M − OH) (Found: M$^+$, 327.2205. $C_{21}H_{29}NO_2$ requires *M*, 327.2198).

In the same way, ketone **3b** (58 mg, 0.19 mmol) and methyllithium (0.16 ml, 0.22 mmol; 1.4 M in diethyl ether) gave a crude product containing no more than 1% **13** by analytical HPLC. Purification by flash chromatography on silica gel (4 : 1 petrol–EtOAc) afforded alcohol **11** (61 mg, 100%).

(*R*$_a$*,1′*R**)-*N*,*N*-Diisopropyl-2-(1′-hydroxy-1′,3′-dimethylbutyl)-1-naphthamide 12

In the same way, ketone **3f** (65 mg, 0.19 mmol) and methylmagnesium bromide (0.08 ml, 0.23 mmol; 3 M in diethyl ether) gave a crude product which ^{1}H NMR showed to be a single diastereoisomer. Flash chromatography (4 : 1 petrol–EtOAc) afforded the *alcohol* **12** (59 mg, 87%) as colourless blades. Mp 120–123 °C (EtOAc); ν_{max}(film)/cm^{-1} 3425, 3061, 2974, 2963, 2936, 2869, 1611; δ_H(300 MHz, CDCl$_3$) 7.9–7.2 (6 H, m, ArH), 3.54 (1 H, septet, *J* 6.5, NCH), 3.52 (1 H, septet, *J* 6.5, NCH), 1.98–1.44 (3 H, m, CH_2CH(CH$_3$)$_2$), 1.69 (3 H, d, *J* 6.5, NCHCH_3), 1.56 (3 H, d, *J* 6.5, NCHCH_3), 1.53 (3 H, s, C(OH)CH_3), 1.08 (3 H, d, *J* 6.5, NCHCH_3), 0.94 (3 H, d, *J* 6.5, CH$_2$CH(CH$_3$)CH_3), 0.90 (3 H, d, *J* 6.5, NCHCH_3) and 0.76 (3 H, d, *J* 6.5, CH$_2$CH(CH$_3$)CH_3); δ_C(75 MHz, CDCl$_3$) 172.7, 142.7, 131.9, 131.2, 130.1, 127.7, 127.6, 126.3, 125.8, 125.4, 124.9, 77.2, 51.4, 50.9, 46.0, 33.0, 25.3, 24.5, 24.3, 20.3, 20.2, 19.7 and 19.6; *m*/*z* (CI) 356 (63%, M + H$^+$) and 338 (100%, M − OH); *m*/*z* (EI) 355 (2%, M$^+$), 197 (81%) and 86 (100%) (Found M$^+$, 355.2517. $C_{23}H_{33}NO_2$ requires *M*, 355.2511).

In the same way, ketone **3f** (65 mg, 0.19 mmol) and methyllithium (0.14 ml, 0.23 mmol; 1.6 M in diethyl ether) gave a crude product which contained (by ^{1}H NMR) a single diastereoisomer. Purification by flash chromatography on silica gel (4 : 1 petrol–EtOAc) afforded alcohol **12** (61 mg, 90%).

(*R*$_a$*,1′*S**)-*N*,*N*-Diisopropyl-2-(1′-hydroxy-1′-methylpropyl)-1-naphthamide 13

In the same way, ketone **3a** (365 mg, 1.23 mmol) and ethylmagnesium bromide (1.48 ml, 1.48 mmol; 1 M in solution in THF) gave a crude product which analytical HPLC showed to contain no more than 1% **11**. Purification by flash chromatography [4 : 1 petrol–EtOAc] afforded the *alcohol* **13** (387 mg, 96%) as a white solid. t_R 5.0 min (4 : 1 hexane–EtOAc); R_f 0.58 (2 : 1 petrol–EtOAc); mp 130–132 °C (EtOAc); λ_{max} (ε_{max}) (CH$_2$Cl$_2$) 232 (43780), 282 (7190); ν_{max}(film)/cm^{-1} 3630–3159, 1609; δ_H(300 MHz, CDCl$_3$) 8.0–7.2 (6 H, m, ArH), 3.63 (1 H, septet, *J* 7, NCH), 3.58 (1 H, septet, *J* 7, NCH), 3.20 (1 H, s, OH), 2.04 (1 H, m, CH_AH$_B$CH$_3$), 1.92 (1 H, m, CH$_A$$H_BCH_3$), 1.80 (3 H, d, *J* 7, NCHCH_3), 1.69 (3 H, d, *J* 7, NCHCH_3), 1.63 (3 H, s, C(OH)CH_3), 1.20 (3 H, d, *J* 7, NCHCH_3), 0.97 (3 H, d, *J* 7, NCHCH_3) and 0.85 (3 H, t, *J* 7, CH$_2$CH_3); δ_C(75 MHz, CDCl$_3$) 172.5, 141.1, 131.9, 131.7, 129.9, 127.8, 127.6, 126.5,

125.9, 125.0, 124.8, 51.3, 46.0, 37.6, 29.4, 20.3, 20.2, 19.5, 19.4 and 7.8; *m*/*z* (CI) 328 (100%, M + H^+) and 310 (58%, M − OH); *m*/*z* (EI) 310 (1%, M − OH) and 86 (100%) (Found M + H^+, 328.2275. $C_{21}H_{29}NO_2$ requires *M* + H, 328.2276).

General procedure for the reduction of ketones with $NaBH_4$

Sodium borohydride (17.5 mg, 0.45 mmol, 3 equiv.) was added to a solution of the ketone (0.15 mmol) in EtOH (4.5 ml) at 0 °C. The mixture was stirred at 0 °C for 16 h. An ice-cold solution of saturated NH_4Cl was added (20 ml) and the mixture extracted with ice-cold CH_2Cl_2 (20 ml × 3). The combined organic fractions were dried at 0 °C (Na_2SO_4) and a small aliquot was removed and stored in the freezer at −18 °C. The ratio of stereoisomers in this sample was analysed by HPLC and is quoted in Table 1. The remainder of the solution was evaporated under reduced pressure, applying no external heating, to yield a crude product in quantitative yield. Analytical HPLC of this material showed a ratio of stereoisomers differing from that observed in the aliquot by a few percent. Comparison of the ^{1}H NMR spectrum of the mixture with those of the known[1] *syn* and *anti* alcohols **6**, **8** and **10** confirmed the sense of the stereoselectivity.

General procedure for the reduction of ketones with $LiBHEt_3$ or $LiBH(s\text{-}Bu_3)$

Lithium triethylborohydride (Superhydride®) or Lithium tri-*sec*-butylborohydride (L-selectride®) (0.16 ml of a 1 M solution in THF, 2 equiv.) was added to a solution of the ketone (0.08 mmol) in THF (1.6 ml) at 0 °C (−40 °C in one case, as indicated in Table 1). The mixture was stirred at 0 °C for 2 h and quenched with an ice-cold solution of NaOH in 30% aqueous hydrogen peroxide (2.5 M in NaOH). The mixture was extracted with ice-cold EtOAc (20 ml × 3). The remainder of the work-up and analysis followed the procedures described for the $NaBH_4$ reductions, and the selectivities are quoted in Table 1.

(R_a*,2′*S)- and (R_a*,2′*R**)-*N*,*N*-Diisopropyl-2-(2′-methyl-3′-phenylpropanoyl)-1-naphthamide *syn*- and *anti*-14.** A solution of ketone **3b** (121 mg, 0.39 mmol) in THF (4 ml) was added to a solution of potassium hexamethyldisilazide (0.78 ml, 0.39 mmol; 0.5 M solution in toluene), in THF (1 ml) at −78 °C under an atmosphere of nitrogen. The mixture was stirred for 30 min and the resulting yellow solution was added to a solution of benzyl bromide (0.23 ml, 1.95 mmol) in THF (2 ml) at −78 °C. After 60 min the reaction was warmed to 20 °C and stirred for a further 30 min. Saturated aqueous ammonium chloride (2 ml) was added, the mixture was extracted with dichloromethane (7 ml × 4) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure without external heating to afford the crude product. Analytical HPLC (4:1 hexane–EtOAc) of the crude product showed the atropisomers to be present in a ratio of 52:48. Purification by flash chromatography (4:1 petrol–EtOAc) afforded a mixture of *ketones* **14** (129 mg, 83%) as a white solid. The mixture was separated by preparative HPLC (8:1 hexane–EtOAc) to afford two samples of diastereoisomerically enriched mixtures containing 75:25 *syn*-**14**:*anti*-**14** and 20:80 *syn*-**14**:*anti*-**14**. t_R^{anti} 3.9 min and t_R^{syn} 5.0 min (4:1 hexane–EtOAc); R_f (2:1 petrol–EtOAc) 0.59; ν_{max}(film)/cm^{-1} 3059, 3025, 2974, 2933, 2873, 1689, 1630; δ_H(300 MHz, $CDCl_3$) 8.05 (1 H, m, ArH), 7.86 (2 H, m, ArH), 7.60 (3 H, m, ArH), 7.35–7.20 (5 H, m, Ph), 3.74 (1 H, m, COCH), 3.67 (1 H, m, NCH), 3.43 (1 H, m, NCH), 3.28 (1 H^{syn}, dd, *J* 13.5 and 6.5, PhC$H_A$$H_B$), 3.22 (1 H^{anti}, dd, *J* 14 and 4.5, PhC$H_A$$H_B$), 2.69 (1 H^{syn}, *J* 14 and 8, Ph$CH_A$$H_B$), 2.64 (1 H^{anti}, dd, *J* 14 and 10, Ph$CH_A$$H_B$), 1.82 (3 H, d, *J* 7, CH_3), 1.81 (3 H^{anti}, d, *J* 7, CH_3), 1.80 (3 H^{syn}, d, *J* 6.5, CH_3), 1.80 (3 H^{syn}, d, *J* 6.5, CH_3), 1.24–1.14 (6 H, m, 2 × CH_3) and 1.01–0.95 (3 H, m, CH_3); δ_C(75 MHz, $CDCl_3$) 205.4, 205.1, 168.7, 140.1, 139.8, 137.2, 136.9, 134.7, 134.6, 131.6, 131.2, 129.7, 129.6, 129.2, 129.2, 128.3, 128.2, 128.0, 127.9, 127.2, 126.6, 126.6, 126.1, 126.0, 124.0, 51.4, 51.3, 46.1, 45.3, 44.9, 38.7, 20.7, 20.7, 20.6, 20.0, 20.0, 19.9, 19.8, 16.7 and 16.0; *m*/*z* (CI) 402 (100%, M + H^+), 401 (3%, M^+) and 49 (100%) (Found: M^+, 401.2354. $C_{27}H_{31}NO_2$ requires *M*, 401.2355).

(R_a*,2′*S)- and (R_a*,2′*R**)-*N*,*N*-Diisopropyl-2-(2′-benzyl-3′-methylbutanoyl)-1-naphthamide *syn*- and *anti*-15.** In the same way, ketone **3f** (160 mg, 0.47 mmol), potassium hexamethyldisilazide (0.94 ml, 0.47 mmol; 0.5 M solution in toluene) and benzyl bromide (0.28 ml, 2.24 mmol) gave, after 6 h at −78 °C and 30 min at 0 °C, a crude mixture of atropisomers which were inseparable by HPLC. ^{1}H NMR showed that the atropisomers were present in a ratio of *ca.* 3:1. Purification by flash chromatography (4:1 petrol–EtOAc) afforded a mixture of the *ketones syn*- and *anti*-**15** (170 mg, 84%) as a white solid. R_f (2:1 petrol–EtOAc) 0.62; ν_{max}(film)/cm^{-1} 3061, 3024, 2962, 2933, 2873, 1686, 1630; δ_H(300 MHz, $CDCl_3$) 8.02 (1 H, m, ArH), 7.82 (1 H, m, ArH), 7.71 (1 H, d, *J* 8.7, ArH), 7.55 (1 H, m, ArH), 7.35 (7 H, m, ArH), 3.67 (1 H^{syn}, septet, *J* 7, NCH), 3.60 (2 H^{anti}, m, NCH and COCH), 3.35 (1 H, m, NCH), 3.27 (1 H^{syn}, dd, *J* 13.5 and 11, PhC$H_A$$H_B$), 3.21 (1 H^{anti}, m, PhC$H_A$$H_B$), 2.88 (1 H^{syn}, dd, *J* 13 and 3, Ph$CH_A$$H_B$), 2.84 (1 H^{anti}, m, Ph$CH_A$$H_B$), 2.25 (1 H^{anti}, m, CHCH(CH_3)$_2$), 2.15 (1 H^{syn}, m, CHCH(CH_3)$_2$), 1.80 (3 H^{anti}, d, *J* 6.5, CH_3), 1.79 (3 H^{syn}, d, *J* 6.5, CH_3), 1.78 (3 H^{syn}, d, *J* 6.5, CH_3), 1.74 (3 H^{anti}, d, *J* 7, CH_3), 1.29 (3 H^{syn}, d, *J* 6.5, CH_3), 1.13 (3 H^{anti}, d, *J* 6.5, CH_3), 1.06 (3 H^{syn}, d, *J* 7, CH_3), 1.01 (6 H^{anti}, d, *J* 7, 2 × CH_3), 1.00 (3 H^{syn}, d, *J* 6.5, CH_3), 0.95 (3 H^{syn}, d, *J* 7, CH_3) and 0.90 (3 H^{anti}, d, *J* 6.5, CH_3); δ_C(75 MHz, $CDCl_3$) 204.4, 168.7, 168.6, 141.3, 140.7, 137.2, 136.4, 134.7, 134.5, 133.0, 131.6, 129.6, 129.5, 129.3, 129.1, 128.3, 128.1, 127.9, 127.9, 127.8, 127.5, 127.0, 126.9, 126.7, 126.6, 125.8, 125.7, 124.6, 123.9, 57.0, 56.5, 51.3, 51.1, 46.1, 46.0, 33.6, 33.1, 30.7, 30.0, 20.9, 20.8, 20.7, 20.6, 20.5, 20.5, 20.0, 19.7, 19.7, 18.9 and 18.7; *m*/*z* (CI) 430 (100%, M + H^+) (Found: M + H, 430.2751. $C_{29}H_{35}NO_2$ requires *M* + H, 430.2746).

Also obtained was *N*,*N*-*diisopropyl-2-[(1′Z)-1′-(benzyloxy)-3′-methylbut-1′-enyl]-1-naphthamide* **18** (21 mg, 6%) as a colourless oil. R_f (2:1 petrol–EtOAc) 0.55; ν_{max}(film)/cm^{-1} 3239, 3063, 2974, 2932, 1721, 1629; δ_H(300 MHz, $CDCl_3$) 7.84 (1 H, d, *J* 9, ArH), 7.75 (1 H, m, ArH), 7.71 (1 H, d, *J* 8.9, ArH), 7.41 (3 H, m, ArH), 7.30–7.10 (5 H, m, ArH), 5.03 (1 H, d, *J* 9, CH=CO), 4.77 (1 H, d, *J* 12, PhC$H_A$$H_B$), 4.37 (1 H, d, *J* 12, Ph$CH_A$$H_B$), 3.47 (2 H, m, 2 × NCH), 2.80 (1 H, d septet, *J* 9 and 6.5, CHCH(CH_3)$_2$), 1.69 (3 H, d, *J* 6.5, CH_3), 1.50 (3 H, d, *J* 6.5, CH_3), 1.04 (3 H, d, *J* 6.5, CH_3), 0.90 (3 H, d, *J* 6.5, CHCH-(CH_3)CH_3), 0.81 (3 H, d, *J* 6.6, CH_3) and 0.73 (3 H, d, *J* 6.7, CHCH(CH_3)CH_3); δ_C(75 MHz, $CDCl_3$) 168.8, 151.0, 137.8, 133.3, 133.2, 130.3, 129.6, 128.8, 128.0, 127.9, 127.8, 127.5, 126.7, 126.6, 126.2, 125.9, 125.7, 72.7, 50.9, 46.0, 25.4, 23.3, 22.8, 21.2, 20.6 and 20.3; *m*/*z* (CI) 430 (32%, M + H^+) and 102 (100%) (Found: M + H^+, 430.2750. $C_{29}H_{35}NO_2$ requires *M* + H, 430.2746).

(R_a*,2′*R) and (R_a*,2′*S**)-*N*,*N*-Diisopropyl-2-(2′,3′-dimethylbutanoyl)-1-naphthamide *syn*- and *anti*-16.** In the same way, ketone **3f** (247 mg, 0.73 mmol) in THF (11 ml), potassium hexamethyldisilazide (0.81 ml of a 0.5 M solution in toluene, 0.41 mmol) in THF (1 ml) and methyl iodide (0.23 ml, 3.64 mmol) gave, after 110 min at −78 °C, a crude product. Analytical HPLC of the crude product showed a 67:33 ratio of atropisomers *syn*-**16**:*anti*-**16**. Purification by flash chromatography (4:1 petrol–EtOAc) afforded a mixture of *ketones* **16** (102 mg, 71%) as a white solid. The mixture was separated by preparative HPLC (6:1 hexane–EtOAc) to afford two samples of diastereoisomerically enriched mixtures containing 74:26 *syn*-**16**:*anti*-**16** and 29:71 *syn*-**16**:*anti*-**16** respectively. t_R^{anti} 5.0

min and t_R^{syn} 6.4 min (6:1 hexane–EtOAc); R_f 0.58 (4:1 petrol–EtOAc); ν_{max}(film)/cm^{-1} 2968, 2932, 2914, 2873, 1686, 1629; δ_H(300 MHz, $CDCl_3$) 8.01 (1 H, m, ArH), 7.89 (2 H, m, ArH), 7.80 (1 H H^{syn}, d, *J* 8.7, ArH), 7.73 (1 H H^{anti}, d, *J* 8.7, ArH), 7.58 (2 H, m, ArH), 3.65 (1 H, m, NCH), 3.44 (1 H, m, NCH), 3.34 (1 H, m, COC*H*CH_3), 2.22 (1 H^{syn}, m, C*H*$CH(CH_3)_2$), 2.12 (1 H^{anti}, m, C*H*$CH(CH_3)_2$), 1.80–1.70 (6 H, m, 2 × CH_3), 1.25 (3 H^{anti}, d, *J* 6.5, CH_3), 1.21 (3 H^{anti}, d, *J* 6.5, CH_3), 1.16 (3 H^{syn}, d, *J* 6.5, CH_3), 1.15 (3 H^{syn}, d, *J* 7, CH_3), 1.05 (3 H^{syn}, d, *J* 6.5, CH_3), 1.00 (3 H^{anti}, d, *J* 7, CH_3), 0.97 (3 H^{anti}, d, *J* 6.5, CH_3), 0.96 (3 H^{syn}, d, *J* 6.5, CH_3), 0.92 (3 H^{syn}, d, *J* 6.6, CH_3) and 0.90 (3 H^{anti}, d, *J* 6.6, CH_3); δ_C(75 MHz, $CDCl_3$) 206.8, 205.7, 168.8, 168.7, 134.6, 134.6, 132.6, 132.2, 129.7, 129.4, 128.1, 127.9, 127.8, 127.8, 127.2, 127.0, 126.6, 126.4, 124.3, 124.2, 51.4, 51.3, 49.5, 48.4, 46.2, 46.1, 30.2, 29.8, 21.6, 21.4, 20.7, 20.6, 20.5, 20.0, 19.9, 19.8, 19.8, 18.0, 17.7 and 11.9; *m*/*z* (CI) 354 (100%, M + H^+) (Found: M + H^+, 354.2433. $C_{23}H_{31}NO_2$ requires *M* + H, 354.2433).

(*R*$_a$*,2′*R)- and (*R*$_a$*,2′*S**)-*N*,*N*-Bis(4-heptyl)-2-(2′-benzyl-3′-methylbutanoyl]-1-naphthamide *syn*- and *anti*-17.** In the same way, ketone **4f** (97 mg, 0.22 mmol), potassium hexamethyldisilazide (0.48 ml, 0.24 mmol; 0.5 M solution in toluene) and benzyl bromide (0.13 ml, 1.08 mmol) gave, after 15 minutes at −78 °C and 2 h at 0 °C, a crude product. Analytical HPLC (20:1 hexane–EtOAc) showed a ratio of 95:5 *syn*-**17**:*anti*-**17**. Purification by flash chromatography on silica gel (10:1 petrol–EtOAc) afforded a mixture of the *ketones syn*- and *anti*-**17** (97 mg, 83%) as a colourless oil (inseparable by preparative HPLC). t_R 10 min (20:1 hexane–EtOAc); ν_{max}(film)/cm^{-1} 3061, 3027, 2959, 2932, 2871, 1682, 1629; δ_H(300 MHz, $CDCl_3$, peaks for *syn*-**17** only) 7.85 (1 H, m, ArH), 7.60 (2 H, m, ArH), 7.44 (1 H, d, *J* 8.5, ArH), 7.34 (2 H, m, ArH), 7.14 (1 H, m, ArH), 7.04–6.90 (3 H, m, ArH), 6.86 (1 H, t, *J* 7, ArH), 3.42 (1 H, dt, *J* 7.5 and 5, COCH), 2.93 (1 H, dd, *J* 14 and 7.5, PhCH_AH$_B$), 2.81 (1 H, m, NCH), 2.62 (1 H, dd, *J* 14 and 5.5, PhCH$_A$$H_B$), 2.59 (1 H, m, NCH), 2.20 (2 H, m, NCH(CH_AH$_B$$CH_2CH_3$)$_2$), 2.06–1.82 (3 H, m, NCH(CH$_A$$H_B$$CH_2CH_3$)$_2$ and C*H*$(CH_3)_2$), 1.40–0.93 (8 H, m, NCH(C$H_2CH_2CH_3$)$_2$ and 4 × NCHCH$_2$CH_AH$_B$-CH_3), 0.92–0.70 (13 H, m, 4 × NCHCH$_2$CH$_A$$H_B$$CH_3$, 2 × NCHCH$_2CH_2CH_3$ and CH(CH_3)CH_3), 0.74 (3 H, d, *J* 7, CH(CH$_3$)CH_3), 0.48 (3 H, t, *J* 7, NCHCH$_2$CH$_2$CH_3) and 0.03 (3 H, t, *J* 7, NCHCH$_2$CH$_2$CH_3); δ_C(75 MHz, $CDCl_3$) 204.5, 169.2, 140.5, 135.9, 134.5, 132.4, 129.7, 129.3, 128.0, 127.9, 127.8, 127.6, 127.3, 126.6, 125.6, 124.6, 59.8, 56.8, 56.4, 36.6, 36.3, 36.0, 35.7, 33.3, 29.8, 21.8, 21.7, 20.7, 20.5, 20.1, 18.9, 14.5, 14.2, 13.8 and 13.1; *m*/*z* (CI) 559 (14%, M + NH_4^+) and 543 (100%); *m*/*z* (EI) 329 (43%, M − NR_2) and 91 (100%) (Found: M + NH_4^+, 559.4239. $C_{37}H_{51}NO_2$ requires *M* + NH_4^+, 559.4263).

The 95:5 mixture of ketones *syn*- and *anti*-**17** were dissolved in ether. After 2 weeks in diethyl ether at ambient temperature the solution contained 17:83 *syn*-**17**:*anti*-**17** (by ^{1}H NMR). The solvent was removed under reduced pressure to yield a colourless oil containing *anti*-**17**. t_R 11.6 min (20:1 hexane–EtOAc); ν_{max}(film)/cm^{-1} 3061, 3028, 2958, 2931, 2871, 1689, 1629; δ_H(300 MHz, $CDCl_3$) 7.80 (1 H, m, ArH), 7.56 (1 H, m, ArH), 7.45 (1 H, d, *J* 8.5, ArH), 7.32 (2 H, m, ArH), 7.07 (3 H, d, *J* 4, ArH), 6.97 (3 H, m, ArH), 3.30 (1 H, ddd, *J* 11, 4.5 and 3, COCH), 3.06 (1 H, dd, *J* 13 and 11, PhCH_AH$_B$), 2.86 (1 H, br m, NCH), 2.60 (2 H, m, NCH and PhCH$_A$$H_B$), 2.10 (2 H, m, 2 × C$H_AH_B$$CH_2CH_3$), 1.94 (3 H, m, 2 × CH$_A$$H_B$$CH_2CH_3$ and C*H*$(CH_3)_2$), 1.50–1.00 (8 H, m, 2 × C$H_2CH_2CH_3$ and 4 × CH_2CH_AH$_B$$CH_3$), 0.91–0.77 (11 H, m, CH(CH_3)CH_3, 2 × CH_2CH_2CH_3 and 2 × CH_2CH$_A$$H_B$$CH_3$), 0.74 (3 H, d, *J* 7, CH(CH$_3$)CH_3), 0.55 (2 H, m, 2 × CH_2CH$_A$$H_B$$CH_3$), 0.47 (3 H, t, *J* 7, CH_2CH_2CH_3) and 0.10 (3 H, t, *J* 7, CH_2CH_2CH_3); δ_C(75 MHz, $CDCl_3$) 204.1, 168.9, 141.5, 136.9, 134.2, 133.1, 129.1, 128.2, 128.0, 127.7, 127.6, 127.5, 127.2, 126.5, 125.8, 123.9, 59.8, 57.4, 57.2, 36.7, 36.4, 36.0, 35.7, 33.6, 30.9, 21.9, 21.6, 20.6, 20.6, 20.3, 18.7, 14.4, 13.9 and 13.4; *m*/*z* (CI) 542 (100%, M + H^+); *m*/*z* (EI) 541 (6%, M^+), 86 (100%), 84 (100%) and 49 (100%) (Found: M^+, 541.3920. $C_{37}H_{51}NO_2$ requires *M*, 541.3920).

***N*,*N*-Diisopropyl-2-{(1′*Z*)-1′-[(trimethylsilyl)oxy]prop-1′-enyl}-1-naphthamide 19.** A solution of ketone **3b** (255 mg, 0.82 mmol) in THF (12 ml) was added to a solution of potassium hexamethyldisilazide (1.80 ml, 0.90 mmol; 0.5 M solution in toluene) in THF (2 ml) at −78 °C under an atmosphere of nitrogen. After 20 minutes, the resulting yellow solution was added *via* a cannula to a solution of chlorotrimethylsilane (0.52 ml, 4.1 mmol), triethylamine (1.1 ml) and THF (2 ml) at −78 °C to give a white suspension. After 10 minutes saturated aqueous sodium hydrogen carbonate (2 ml) was added and the mixture was extracted with diethyl ether (10 ml × 4). The combined organic extracts were washed with water (20 ml) and aqueous 0.1 M citric acid (20 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the *silyl enol ether* **19** (292 mg, 93%) as a white solid. Mp 100–101 °C; ν_{max}(film)/cm^{-1} 3057, 2965, 2930, 2874, 2859, 1630; δ_H(300 MHz, $CDCl_3$) 7.77 (1 H, d, *J* 7.5, ArH), 7.66 (1 H, d, *J* 7, ArH), 7.62 (1 H, d, *J* 8.5, ArH), 7.34 (3 H, m, ArH), 5.14 (1 H, q, *J* 7, C=C*H*CH_3), 3.44 (2 H, m, 2 × NCH), 1.65 (3 H, d, *J* 6.5, NCHCH_3), 1.62 (3 H, d, *J* 7, NCHCH_3), 1.51 (3 H, d, *J* 6.5, C=CHCH_3), 0.98 (3 H, d, *J* 6.5, NCHCH_3), 0.75 (3 H, d, *J* 6.5, NCHCH_3) and 0.00 (9 H, s, $SiMe_3$); δ_C(75 MHz, $CDCl_3$) 168.8, 149.4, 133.2, 132.9, 132.6, 130.2, 127.7, 127.6, 126.6, 125.9, 125.7, 125.4, 109.2, 50.7, 45.9, 21.3, 20.5, 11.6 and 0.4; *m*/*z* (CI) 384 (65%, M + H^+) and 312 (100%); *m*/*z* (EI) 383 (4%, M^+) and 73 (100%) (Found: M^+, 383.2279. $C_{23}H_{33}NO_2Si$ requires *M*, 383.2280).

***N*,*N*-Diisopropyl-2-{(1′*Z*)-3′-methyl-1′-[(trimethylsilyl)oxy]-but-1′-enyl}-1-naphthamide 20.** In the same way, ketone **3f** (261 mg, 0.77 mmol), potassium hexamethyldisilazide (1.70 ml, 0.85 mmol; 0.5 M solution in toluene), chlorotrimethylsilane (0.49 ml, 3.85 mmol), and triethylamine (1.1 ml) gave, after purification by flash chromatography on neutral alumina (15:1 petrol–EtOAc) the silyl enol ether **20** (301 mg, 95%) as a sticky white solid. R_f (15:1 petrol–EtOAc) 0.41; ν_{max}(film)/cm^{-1} 3057, 2963, 2933, 2905, 2868, 1642, 1632; δ_H(300 MHz, $CDCl_3$) 7.81 (1 H, d, *J* 7.5, ArH), 7.68 (1 H, m, ArH), 7.64 (1 H, d, *J* 8, ArH), 7.41 (1 H, d, *J* 8.5, ArH), 7.36 (2 H, m, ArH), 4.95 (1 H, d, *J* 9.5, C*H*$CH(CH_3)_2$), 3.45 (2 H, m, 2 × NCH), 2.78 (1 H, d septet, *J* 9.5 and 6.5, CHC*H*$(CH_3)_2$), 1.69 (3 H, d, *J* 6.5, CH_3), 1.57 (3 H, d, *J* 6.5, CH_3), 1.03 (3 H, d, *J* 6.5, CH_3), 1.00 (3 H, d, *J* 6.5, CH_3), 0.96 (3 H, d, *J* 6.5, CH_3), 0.77 (3 H, d, *J* 6.5, CH_3) and 0.00 (9 H, s, Si$(CH_3)_3$); δ_C(75 MHz, $CDCl_3$) 168.8, 146.8, 133.2, 132.8, 132.6, 130.2, 127.7, 127.5, 126.5, 126.2, 125.9, 125.7, 122.2, 50.8, 45.9, 25.4, 23.4, 22.9, 21.3, 21.2, 20.8, 20.6 and 0.4; *m*/*z* (CI) 412 (100%, M + H^+); *m*/*z* (EI) 411 (6%, M^+) and 49 (100%) (Found: M^+, 411.2597. $C_{25}H_{37}NO_2Si$ requires *M*, 411.2953).

(*R*$_a$*,1′*R,2′*R**)- and (*R*$_a$*,1′*R**,2′*S**)-*N*,*N*-Bis(4-heptyl)-2-(1′-hydroxy-3′-methyl-2′-(phenylmethyl)butyl)-1-naphthamide 21 and 22.** By the general procedure given above, the 17:83 mixture of ketones *syn*- and *anti*-**17** (66 mg, 0.12 mmol) in THF (2 ml) were treated with $LiBHEt_3$ (0.31 ml, 0.31 mmol; 1 M solution in THF) to yield a crude product (64 mg, 97%) containing, by analytical HPLC, two diastereoisomers **21** and **22** in a ratio of 25:75. Purification by preparative HPLC (30:1 hexane–EtOAc) gave the *alcohol* **21**. t_R 7.3 min (30:1 hexane–EtOAc); ν_{max}(film)/cm^{-1} 3064, 3027, 3015, 2990, 2973, 2959, 2934, 2881, 1717; δ_H(300 MHz, $CDCl_3$) 7.80 (1 H, m, ArH), 7.60 (1 H, m, ArH), 7.39 (2 H, m, ArH), 7.20 (2 H, m, ArH), 6.73 (1 H, m, ArH), 6.64 (4 H, m, ArH), 4.79 (1 H, dd, *J* 9 and 3.5, C*H*OH), 2.97 (2 H, m, 2 × NCH), 2.41 (2 H, d, *J* 5.5, CH_2Ph), 2.25 (2 H, m, CH_AH$_B$$CH_2CH_3$ and CH(OH)C*H*), 2.12–1.80 (3 H, m, 3 × CH_AH$_B$$CH_2CH_3$), 1.54–0.74 (26 H, m,

4 × $CH_AH_BCH_2CH_3$, 4 × $CH_2CH_2CH_2CH_3$, $CH(CH_3)_2$, CHOH and 2 × $CH_2CH_2CH_2CH_3$), 0.69 (3 H, t, *J* 6.5, $CH_2CH_2CH_3$) and 0.26 (3 H, t, *J* 7, $CH_2CH_2CH_3$); δ_C(75 MHz, $CDCl_3$) 169.6, 142.5, 136.4, 132.7, 128.8, 128.5, 128.3, 127.9, 127.6, 127.2, 126.0, 126.0, 125.9, 124.3, 123.7, 73.0, 59.7, 56.8, 37.1, 36.3, 35.2, 30.9, 27.6, 21.9, 21.8, 20.9, 20.4, 17.6, 14.5, 14.4, 14.0 and 13.2; *m*/*z* (CI) 544 (100%, M + H^+); *m*/*z* (EI) 543 (3%, M^+), 397 (88%, M − $C_{11}H_{15}$) and 183 (100%) (Found: M^+, 543.4065. $C_{37}H_{53}NO_2$ requires *M*, 543.4076).

Also obtained was the *alcohol* **22**. t_R 10.5 min (30 : 1 hexane–EtOAc); ν_{max}(film)/cm^{-1} 3058, 3047, 3016, 2994, 2973, 2933, 1717; δ_H(300 MHz, $CDCl_3$) 7.81 (1 H, dd, *J* 9 and 2, ArH), 7.70 (2 H, m, ArH), 7.52 (1 H, d, *J* 8.5, ArH), 7.40 (2 H, m, ArH), 7.16–7.00 (5 H, m, ArH), 5.06 (1 H, dd, *J* 6 and 3.5, CHOH), 2.96 (1 H, br m, NCH), 2.89 (1 H, quintet, *J* 6.5, NCH), 2.76 (2 H, d, *J* 6.5, CH_2Ph), 2.40 (1 H, m, $CH_AH_BCH_2CH_3$), 2.23 (2 H, m, CH(OH)CH and $CH_AH_BCH_2CH_3$), 1.98 (2 H, m, $CH_2CH_2CH_3$), 1.60–0.80 (12 H, m, $CH(CH_3)_2$, 3 × CH_2CH_2-CH_3, 2 × $CH_2CH_2CH_3$ and OH), 0.97 (3 H, t, *J* 7.5, CH_2-CH_2CH_3), 0.96 (3 H, t, *J* 7.5, $CH_2CH_2CH_3$), 0.88 (3 H, d, *J* 6.5, $CH(CH_3)CH_3$), 0.86 (3 H, d, *J* 7, $CH(CH_3)CH_3$), 0.66 (3 H, t, *J* 7.5, $CH_2CH_2CH_3$), 0.63 (2 H, m, $CH_2CH_2CH_3$) and 0.17 (3 H, t, *J* 7.5, $CH_2CH_2CH_3$); δ_C(75 MHz, $CDCl_3$) 169.4, 142.4, 136.9, 132.9, 132.6, 129.6, 128.8, 128.3, 128.0, 127.7, 126.1, 126.0, 126.0, 125.6, 123.9, 74.5, 59.8, 56.9, 52.1, 37.0, 36.8, 36.2, 35.5, 32.6, 28.8, 21.9, 21.7, 21.1, 20.4, 20.1, 18.9, 14.4, 14.1 and 13.1; *m*/*z* (CI) 544 (100%, M + H^+); *m*/*z* (EI) 543 (3%, M^+), 397 (53%, M − $C_{11}H_{15}$), 396 (29%, M − $C_{11}H_{16}$) and 183 (100%) (Found: M^+, 543.4059. $C_{37}H_{53}NO_2$ requires *M*, 543.4076).

Crystal data for 13§

Single crystals of **13** were grown from ethyl acetate, mounted on a thin glass fibre and transferred to the cold gas stream of the diffractometer. $C_{21}H_{29}NO_2$, $M = 327.47$. Orthorhombic, $a = 12.404(1)$, $b = 19.6149(8)$, $c = 16.222(2)$ Å, $V = 3947.1(5)$ $Å^3$, $T = 295$ K, space group *Pbca* (no. 61), $Z = 8$, $D_c = 1.102$ g cm^{-3}, μ(Cu-Kα) = 5.5 cm^{-1}. Data collected on a Rigaku AFC5R diffractometer, 4572 reflections measured, 2892 unique. Final agreement factors for 218 parameters gave $R_1 = 0.057$, $wR^2 = 0.045$. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.24 and −0.20 e $Å^{-3}$, respectively. All calculations were performed using the teXsan crystallographic software package of Molecular Structure Corporation.[55] Most hydrogen atoms were located by difference Fourier techniques and refined isotropically to convergence. For the last round of refinement, they were fixed in their final positions. Hydrogen atoms bonded to C19 were placed in calculated positions and not refined.

Crystal data for 3e§

Single crystals of **3e** were grown from ethyl acetate, mounted on a thin glass fibre and transferred to the cold gas stream of the diffractometer. $C_{24}H_{25}NO_2$, $M = 327.47$. Monoclinic, $a = 7.6743(9)$, $b = 24.817(4)$, $c = 10.629(1)$ Å, $\beta = 101.216(9)°$, $V = 1985.6(5)$ $Å^3$, F_{000} 768, $\lambda = 0.710\ 69$ Å, $T = 20.0$ °C, space group $P2_1/n$ (no. 14), $Z = 4$, $D_{calc} = 1.202$ g cm^{-3}, μ(Mo-Kα) = 0.7 cm^{-1}. Data collected on a Rigaku AFC5R diffractometer. A total of 3896 reflections was collected, of which 3615 were unique ($R_{int} = 0.49$). Final agreement factors for 244 parameters gave $R_1 = 0.051$, $wR^2 = 0.050$. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.19 and −0.20 e $Å^{-3}$, respectively. All calculations were performed using the teXsan crystallographic software package of Molecular Structure Corporation.[55]

§ CCDC reference number 207/412. See http://www.rsc.org/suppdata/p1/b0/b000668h for crystallographic files in .cif format.

Acknowledgements

We are grateful to the EPSRC and Roche Discovery (Welwyn) for a CASE award (to N. W.), to Zeneca for an unrestricted grant, to the Royal Society for an Equipment Grant, and to Dr Francis Wilson for helpful discussions.

References

1 P. Bowles, J. Clayden, M. Helliwell, C. McCarthy, M. Tomkinson and N. Westlund, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2607.
2 J. H. Ackerman, G. M. Laidlaw and G. A. Snyder, *Tetrahedron Lett.*, 1969, 3879.
3 P. M. van Lier, G. H. W. M. Meulendijks and H. M. Buck, *Recl. Trav. Chim. Pays-Bas*, 1983, **102**, 337.
4 M. A. Cuyegkeng and A. Mannschreck, *Chem. Ber.*, 1987, **120**, 803.
5 W. H. Pirkle, C. J. Welch and A. J. Zych, *J. Chromatogr.*, 1993, **648**, 101.
6 A. Ahmed, R. A. Bragg, J. Clayden, L. W. Lai, C. McCarthy, J. H. Pink, N. Westlund and S. A. Yasin, *Tetrahedron*, 1998, **54**, 13277.
7 P. Bowles, J. Clayden and M. Tomkinson, *Tetrahedron Lett.*, 1995, **36**, 9219.
8 R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, 1994.
9 C. Rosini, L. Franzini, A. Raffaelli and P. Salvadori, *Synthesis*, 1992, 503.
10 K. Tanaka, M. Ahn, Y. Watanabe and K. Fuji, *Tetrahedron: Asymmetry*, 1996, **7**, 1771.
11 K. Fuji, M. Node, F. Tanaka and S. Hosomi, *Tetrahedron Lett.*, 1989, **30**, 2825.
12 K. Fuji, M. Node and F. Tanaka, *Tetrahedron Lett.*, 1990, **31**, 6553.
13 K. Fuji, F. Tanaka and M. Node, *Tetrahedron Lett.*, 1991, **32**, 7281.
14 F. Tanaka, M. Node, K. Tanaka, M. Mizuchi, S. Hosoi, M. Nakayama, T. Taga and K. Fuji, *J. Am. Chem. Soc.*, 1995, **117**, 12159.
15 K. Fuji, K. Tanaka, M. Mizuchi and S. Hosoi, *Tetrahedron Lett.*, 1991, **32**, 7277.
16 K. Fuji, X.-S. Yang, K. Tanaka, N. Asakawa and X.-J. Hao, *Tetrahedron Lett.*, 1996, **37**, 7373.
17 Y. Tamai, S. Koike, A. Ogura and S. Miyano, *J. Chem. Soc., Chem. Commun.*, 1991, 799.
18 K. Fuji, K. Tanaka, M. Ahn and M. Mizuchi, *Chem. Pharm. Bull.*, 1994, **42**, 957.
19 Y. Tamai, M. Akiyama, A. Okamura and S. Miyano, *J. Chem. Soc., Chem. Commun.*, 1992, 687.
20 Y. Tamai, T. Hattori, M. Date, H. Takayama, Y. Kamikubo, Y. Minato and S. Miyano, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1141.
21 G. Delogu, L. de Lucchi and P. Maglioli, *Synlett*, 1989, 28.
22 G. Delogu, L. de Lucchi, P. Maglioli and G. Licini, *J. Chem. Soc., Chem. Commun.*, 1989, 411.
23 K. Ohmori, M. Kitamura and K. Suzuki, *Angew. Chem., Int. Ed.*, 1999, **38**, 1226.
24 K. Ohmori, M. Kitamura and K. Suzuki, *Angew. Chem., Int. Ed.*, 1999, **38**, 1229.
25 N. Taniguchi, T. Hata and M. Uemura, *Angew. Chem., Int. Ed.*, 1999, **38**, 1232.
26 S. Cossu, G. Delogu, O. de Lucchi, D. Fabbri and G. Licini, *Angew. Chem., Int. Ed. Engl.*, 1982, **28**, 766.
27 S. Miyano, M. Tobita and H. Hashimoto, *Bull. Chem. Soc. Jpn.*, 1981, **54**, 5322.
28 S. Miyano, H. Fukushima, S. Handa, H. Ito and H. Hashimoto, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 3249.
29 Y. Kawakami, J. Hiratake, Y. Yamamoto and J. Oda, *J. Chem. Soc., Chem. Commun.*, 1984, 779.
30 A. Martin, M.-P. Jouannetaud, J.-C. Jacquesy and A. Cousson, *Tetrahedron Lett.*, 1996, **37**, 7735.
31 R. W. Baker, T. W. Hambley and P. Turner, *J. Chem. Soc., Chem. Commun.*, 1995, 2509.
32 T. Kawamoto, M. Tomishima, J. Kunimoto, F. Yoneda and J.-i. Hayami, *Tetrahedron Lett.*, 1992, **33**, 7173.
33 T. Kawamoto, M. Tomishima, F. Yoneda and J.-i. Hayami, *Tetrahedron Lett.*, 1992, **33**, 3173.
34 A. Ohno, S. Oda and N. Yamazaki, *Tetrahedron Lett.*, 1999, **40**, 4577.
35 A. Ohno, Y. Ishikawa, N. Yamazaki, M. Okanawa and Y. Kawai, *J. Am. Chem. Soc.*, 1998, **120**, 1186.
36 J. Clayden, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 949.

37 A. D. Hughes, D. A. Price and N. S. Simpkins, *J. Chem. Soc.*, *Perkin Trans. 1*, 1999, 1295.
38 A. D. Hughes and N. S. Simpkins, *Synlett*, 1998, 967.
39 M. Fujita, O. Kitagawa, H. Izawa, A. Dobashi, H. Fukaya and T. Taguchi, *Tetrahedron Lett.*, 1999, **40**, 1949.
40 D. P. Curran, G. R. Hale, S. J. Geib, A. Balog, Q. B. Cass, A. L. G. Degani, M. Z. Hernandes and L. C. G. Freitas, *Tetrahedron: Asymmetry*, 1997, **8**, 3955.
41 D. P. Curran, S. Geib and N. DeMello, *Tetrahedron*, 1999, **55**, 5681.
42 O. Kitagawa, H. Izawa, T. Taguchi and M. Shiro, *Tetrahedron Lett.*, 1997, **38**, 4447.
43 O. Kitagawa, H. Izawa, K. Sato, A. Dobashi and T. Tagichi, *J. Org. Chem.*, 1998, **63**, 2634.
44 Preliminary communication: J. Clayden, N. Westlund and F. X. Wilson, *Tetrahedron Lett.*, 1996, **37**, 5577. For examples of similar reactions of compounds with planar chirality, see E. V. Sergeeva, V. I. Rozenberg, E. V. Vorontsov, T. I. Danilova, Z. A. Starikova, A. I. Yanovsky, Y. N. Belokon and H. Hopf, *Tetrahedron: Asymmetry*, 1996, **7**, 3445; N. Kanomata and T. Nakata, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1207.
45 Preliminary communication: J. Clayden, M. Darbyshire, J. H. Pink, N. Westlund and F. X. Wilson, *Tetrahedron Lett.*, 1997, **38**, 8487.
46 J. Clayden, C. McCarthy, N. Westlund and C. S. Frampton, *J. Chem. Soc.*, *Perkin Trans. 1*, 2000, DOI: 10.1039/b000669f.
47 J. Clayden, N. Westlund and C. S. Frampton, *J. Chem. Soc.*, *Perkin Trans. 1*, 2000, DOI: 10.1039/b000670j.
48 V. Snieckus, *Chem. Rev.*, 1990, **90**, 879.
49 Attempts to form the ketones directly by addition of ortholithiated amides to acyl chlorides failed, but recently we have found that similar ketones may conveniently be produced in low, but acceptable, yields using *N*,*N*-dimethylcarboxamides as electrophiles: J. Clayden and L. W. Lai, unpublished results.
50 D. A. Evans, in *Asymmetric Synthesis*, ed. J. D. Morrison, Academic Press, New York, 1984, vol. 3, p. 2.
51 A. D. Hughes, D. A. Price, O. Shishkin and N. S. Simpkins, *Tetrahedron Lett.*, 1996, **37**, 7607.
52 A. I. Meyers, J. R. Flisak and R. A. Aitken, *J. Am. Chem. Soc.*, 1987, **109**, 5446; J. Clayden and L. W. Lai, *Angew. Chem., Int. Ed.*, 1999, **38**, 2556.
53 F. Mohmadi, N. G. J. Richards, W. C. Guida, R. Liskamp, M. Lipton, C. Caufield, G. Chang, T. Hendrickson and W. C. Still, *J. Comput. Chem.*, 1990, **11**, 440.
54 W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.
55 teXsan: Crystal Structure Analysis Package, Molecular Structure Corporation (1985 and 1992).