Pergamon

Tetrahedron 55 (1999) 14161–14184

TETRAHEDRON

Perilithiation and the Synthesis of 8-Substituted-1-Naphthamides

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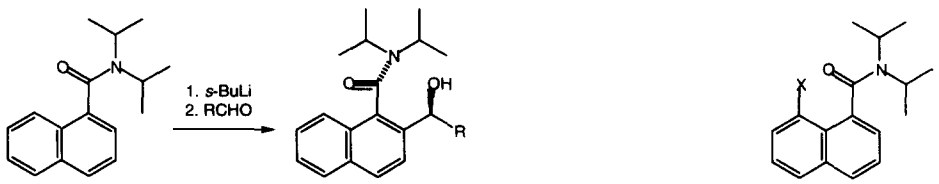
Received 19 August 1999; revised 10 September 1999; accepted 30 September 1999

Abstract: Attempted perilithiation of 1-naphthamides with their 2-positions blocked leads only to nucleophilic attack on the aromatic ring, but perilithiation of naphthalenes bearing 1-substituents such as $-NMe_2$ or $-CH_2NMe_2$ allows the synthesis of 8-substituted-1-naphthamides. The 8-CH_2NMe_2 substituents can be converted to carbonyl groups by Polonovski reactions; other 8-substituents may be introduced by using naphthalic anhydride as a starting material.

Keywords: Amides, Lithiation, Naphthalenes, Polonoski reaction

Introduction

Two features of aromatic tertiary amide substituents place them among the best directors of ortholithiation:[1] electron-withdrawing ability, which acidifies the protons of the aromatic ring, and the basicity of their carbonyl groups, which coordinate to organolithiums and direct them to deprotonate the ortho positions.[2-5] Aromatic tertiary amides may also have stereochemistry if they are twisted out of the plane of the aromatic ring,[6] and we have exploited both the regioselectivity and the stereoselectivity of the lithiation–electrophilic quench of 1-naphthamides **1** in an atroposelective synthesis of diastereoisomeric alcohols **2**.[7]



1 2 3

Scheme 1: Regio- and stereoselectivity in the lithiation-electrophilic quench of a 1-naphthamide

As part of our continuing programme of research into the conformational stability[8] and stereoselective reactions[9] of rotationally restricted tertiary amides, we needed some 8-substituted amides **3**, which we hoped to make by directed perilithiation reactions. In this paper, we describe the synthesis of a range of amides **3** both by perilithiation and by some alternative routes starting from available 1,8-disubstituted naphthalenes.

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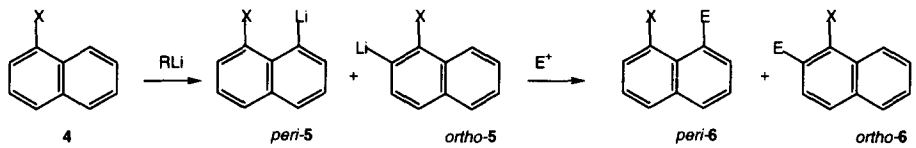
0040-4020/99/$ - see front matter
PII: S0040-4020(99)00881-9

Attempted perilithiation of 1-naphthamides

A few perilithiations have been reported, but many are low-yielding and suffer from lack of regioselectivity with respect to competing ortholithiation (Scheme 2 and Table 1).[10] The best perilithiation-directing groups are those which (a) coordinate to the incoming organolithium but (b) do not acidify nearby protons, thereby disfavouring directed ortholithiation. Typical perilithiation substrates are therefore naphthalenes bearing electron-rich oxygen or nitrogen-based substituents, but even among those there is considerable variation, with several (OMe or OMOM with *n*-BuLi, TMEDA, for example) giving only *ortho*-substituted products **6**. The highest yields of *peri*-substituted products are obtained from naphthalenes **4** bearing X = NMe_2 or CH_2NMe_2. Regiochemistry may change with base, and with reaction time.[11]



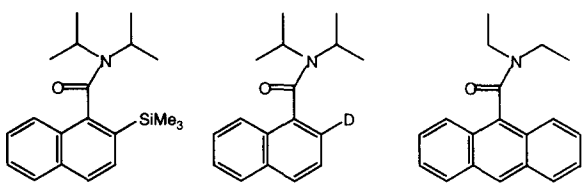
Scheme 2: Peri/ortho regioselectivity in lithiation reactions

Table 1

entry	**4**, X =	conditions	E^+ =	yield *peri*-**6**	yield *ortho*-**6**	ref.
1	OH	*n*-BuLi, THP, 50 °C, 4 h	Me_2S_2	50	19	12
2	OH	*t*-BuLi, TMEDA, 20 °C	various	[a]	0	13
3	OMe	*t*-BuLi, cyclohexane, 20 °C, 26 h	CO_2	35	0	14
4	OMe	*n*-BuLi, TMEDA, 20 °C	CO_2	0	59	14
5	OMOM	*n*-BuLi, TMEDA	RCHO	0	73	15
6	$OCONR_2$	*s*-BuLi, TMEDA, THF, –78 °C	MeI	0	90	5
7	NH_2	*n*-BuLi × 3, Et_2O, Δ, 50 h	CO_2	20	0	16
8	NMe_2	*n*-BuLi, Et_2O, 20 °C, 48 h	DMF	76	0	17,18
9	NLiR	*t*-BuLi, Et_2O, 20 °C	D_2O	[a]	0	19
10	CH_2NMe_2	*n*-BuLi, Et_2O, hexane, 20 °C, 24 h	Ph_2CO	58 (91)[b]	0 (9)[b]	20
11	$CH(OMe)_2$	*t*-BuLi, Et_2O, 0 °C	MeI	27[c]	13[c]	21
12	$CH(NEt_2)OLi$	*n*-BuLi, PhH, Δ, 10 h	DMF	32[c]	2[c]	21
13	$CONEt_2$	*s*-BuLi, TMEDA, THF, –78 °C	Me_3SiCl	0	80	5
14	CON*i*-Pr_2	*s*-BuLi, THF, –78 °C	Me_3SiCl	0	76	7
15	CON*i*-Pr_2	*s*-BuLi, THF, –78 °C	D_2O	0	93	this work

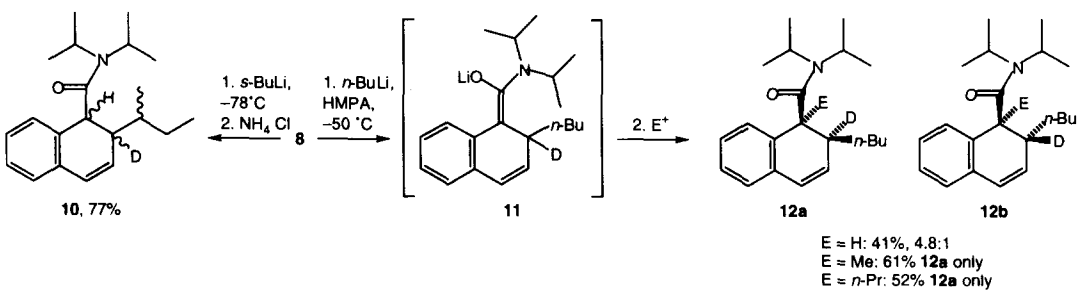
[a]Sole product; [b]Ratio in crude product, by ^1H NMR; [c]GC yield

With electron withdrawing substituents such as X = $CONR_2$, *ortho*-**5** becomes the kinetic and the thermodynamic product.[5] The unstable (presumably with respect to transfer of lithium to the ortho position) 8-lithio-1-naphthamides **3** (X = Li) have been made by bromine-lithium exchange from 8-bromo-1-naphthamides,[22] themselves available in several steps from naphthalic anhydride.[23] But we hoped that direct perilithiation of a naphthamide whose 2-position is blocked by another substituent would provide the simplest way of introducing an 8-substituent. We made three 2-substituted naphthamides as starting materials: 2-trialkylsilyl substituted **7**[7] and 2-deuterated **8** (by ortholithiation: see Table 1, entries 14 and 15), and 9-anthracenecarboxamide **9** (from 9-anthracenecarboxylic acid by standard methods). Treatment of **7** with *s*-BuLi or *t*-BuLi failed to lithiate it, and it has recently become clear that 2-trialkylsilyl-1-naphthamides lithiate α to silicon and not at the *peri* position.[24,25]



7 **8** **9**

We hoped that at –78 °C the kinetic isotope effect would have a value sufficiently large[26] that the usually rapid ortholithiation of **1** might be slowed sufficiently in **8** to allow alternative reactions not involving *ortho*-deprotonation, such as perilithiation. We have previously employed this strategy as a means of controlling the regiochemistry of lithiation.[27] In the event, treatment of **8** with *s*-BuLi led to a different competing pathway: addition of the organolithium to the naphthalene ring to give a 1:4:6:9 mixture of the four diastereoisomers of **10** in 77% yield after 70 min (Scheme 3).



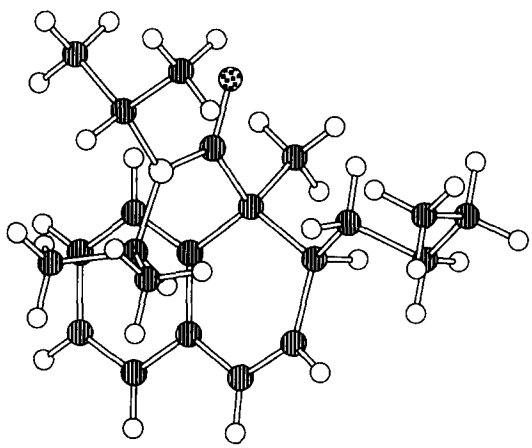
Scheme 3: Additions to a deuterated naphthamide

Starting material recovered from the reaction in 20% yield was only 52% deuterated: about 10% of **8** must therefore have been lithiated at the 2-position, so the rate of ortholithiation of **8** appears to be about 1/8 of the rate of ring addition. Given that ortholithiation of **1** is usually at least 10 times as fast as addition of *s*-BuLi

to the ring of **1** (ring addition is not a reported side reaction in naphthamide ortholithation) we can estimate a value for the primary kinetic isotope effect for ortholithiation of **1** or **8** (assuming the secondary kinetic isotope effect on the addition is 1) of $k_H/k_D > 80$ at –78 °C. This is of the same order of magnitude as the kinetic isotope effects reported for other low-temperature lithiations.[26,27]

We tried other organolithiums and found that MeLi ortholithiated **8** to some extent at temperatures above 0 °C (aqueous quench returned 55:45 **8**:**1** in 42% yield after 16 h at 20 °C), but gave <2% addition to the ring. *t*-BuLi gave 5% addition to the ring after 1 h at –78 °C, along with 24% recovered starting material, 70:30 **8**:**1**. Raising the temperature or adding HMPA gave intractable mixtures of products.

n-BuLi did not react with **8** at –78 °C, but at –50 °C in the presence of HMPA it too added to the ring, giving **12** (E = H) as a 4.8:1 mixture of diastereoisomers **12a** and **12b** in 41% yield. Reaction times in excess of 16 h were required to get reasonable yields, but raising the temperature above –40 °C reduced the magnitude of kinetic isotope effect to the point where ortholithiation became the major reaction pathway (recovered starting material was more **1** than **8**). However, when the intermediate enolate **11** was quenched with MeI or *n*-PrI, the alkylated dihydronaphthalenes **12a** (E = Me, *n*-Pr) were obtained as single diastereoisomers in 61% and 52% yields respectively.



12a (E = Me)

Figure 1: X-ray crystal structure of ***12a*** *(E = Me)*

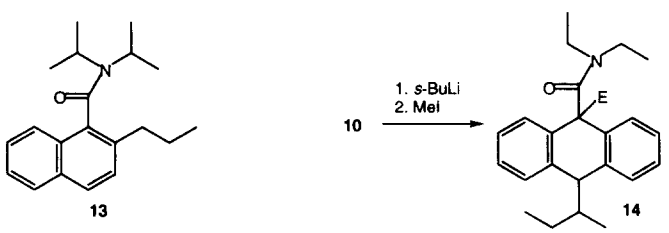
Relative stereochemistry was assigned to **12a** (E = Me) from its X-ray crystal structure (Figure 1), and we assumed the same *syn* stereochemistry for **12a** (E = *n*-Pr). To determine the stereochemistry of **12** (E = H) we repeated the addition with **8**'s undeuterated analogue **1** and obtained a mixture of diastereoisomers of undeuterated **12** in 20% yield. Irradiation of the proton H-2 in the diastereoisomer corresponding spectroscopically and chromatographically to **12a** (E = H) gave a 7.5% NOE at H-1. We presume that the

preferential formation of **12a** is due to the approach of the electrophile to the less hindered face of the enolate, *trans* to *n*-Bu, and that the stereoselectivity of formation of **12a** (E = H) is under kinetic control.[28]

The formation of **12a** (E = Me) was accompanied by 15% of **1** (undeuterated starting material) while that of **12a** (E = *n*-Pr) was accompanied by 10% of **1** and 11% of the *ortho*-alkylated naphthamide **13**. By the same argument as for *s*-BuLi, these by-products suggest that ortholithiation with *n*-BuLi–HMPA at –50 °C is some 25% - 50% as fast as addition to the ring. Since addition to the ring does take place with *n*-BuLi–HMPA in 20% yield, the primary kinetic isotope effect k_H/k_D appears to be rather lower in this case: of the order of 10 - 20.

The dearomatising addition of organolithiums to the 1-position of naphthalene is known.[29] Dearomatising addition to the 2-position of naphthalene rings bearing electron-withdrawing substituents in the 1-position is also well-precedented, particularly for naphthyloxazolines[30-34] and naphthylimines.[35] Organolithiums have been added to the ring of naphthalene-1-carboxylates,[36] to very bulky 2,6-di-*tert*-butylphenyl esters of 1-naphthoic acid,[37] and to aromatic aldehydes and ketones complexed with bulky Lewis acids.[38,39] We have demonstrated the intramolecular dearomatising cyclisation of organolithiums onto naphthamides[40] and benzamides,[41] and we have also made sporadic observations of ring-addition by-products from lithiations, especially in the presence of HMPA or DMPU or when the groups on nitrogen are either very large[7] or small.[42]

The same addition reaction prevented lithiation of the anthracenecarboxamide **10**. The only products isolated from the treatment of **10** with *s*-BuLi then MeI contained, by mass spectroscopy, an additional butyl group, and were tentatively identified as a mixture of the diastereoisomers of **14** with E = Me or E = H (Scheme 4).

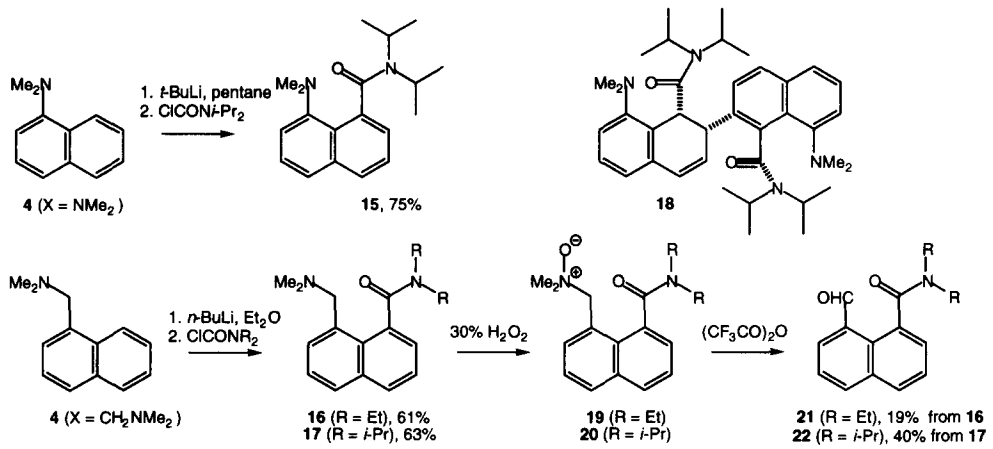


Scheme 4: Attempted lithiation of a 9-anthracenecarboxamide

Introduction of the amide substituent by perilithiation

We next turned to the lithiation of starting materials **4** already bearing the 8-substituent X, which we hoped to be able to modify by subsequent chemistry. Lithiations of **4** (X = NMe_2)[17] and **4** (X = CH_2NMe_2)[20] are known (see Table 1), and treatment of **4** (X = NMe_2) with *n*-BuLi in ether or **4** (X = CH_2NMe_2) with *t*-BuLi in pentane (we found *t*-BuLi gave better results than the literature method using *n*-BuLi) for 24 h gave the corresponding organolithiums *peri*-**5**. These were added to *N,N*-diisopropyl or *N,N*-diethylcarbamyl chloride to give the 8-substituted 1-naphthamides **15**, **16** and **17**, without the need for transmetallation with Cu or Mn described for the

synthesis of the similar thioamides[18]. It was important to add a suspension of the perilithiated amine to the carbamyl chloride: reversing the addition with *peri*-**5** (X = NMe_2) led to competing formation of **18**.[43]

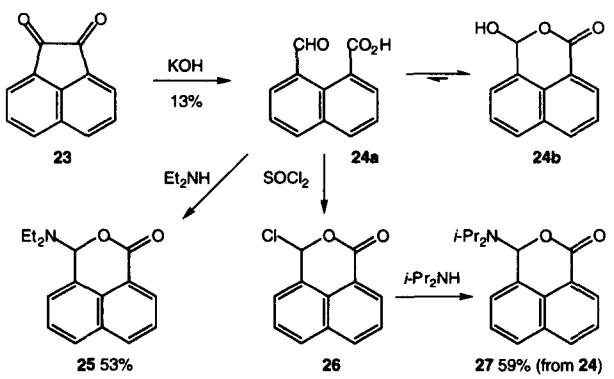


Scheme 5: Synthesis of 8-substituted-1-naphthamides by perilithiation

The *N,N*-dimethylaminomethyl substituents of **16** and **17** are amenable to further elaboration because their *N*-oxides can be used as the substrate for Polonovski reactions. We treated **16** and **17** with 30% H_2O_2 to form the *N*-oxides **19** and **20**. These both rearranged in poor to moderate yield with trifluoroacetic anhydride to give the valuable[44] aldehydes **21** and **22**.

Synthesis of 1,8-disubstituted naphthamides from 1,8-disubstituted starting materials

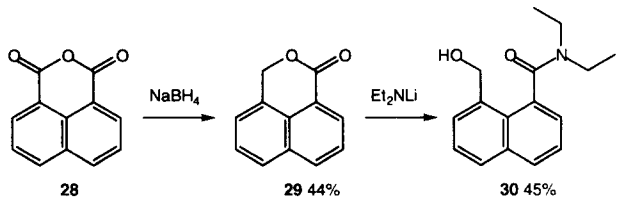
An alternative, apparently simpler, route to 8-substituted naphthamides – particularly with 8-alkyl or 8-acyl substituents – would exploit the substitution pattern of an available 1,8-disubstituted naphthalene. However, apparently simple reactions of this type of compound are complicated by the proximity of the 1- and 8-substituents.[17,45]



Scheme 6: Routes from acenaphthenequinone

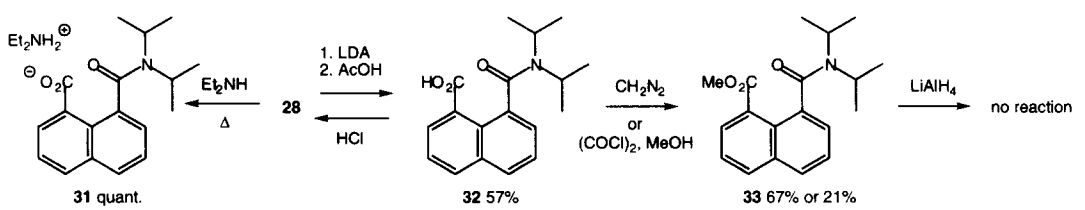
The obvious starting point for a synthesis of the 8-formyl naphthamides **21** and **22** is "1,8-naphthaldehydic acid" **24**, available in low yield from acenaphenequinone **23**[46] and existing mainly as the anhydride lactol **24b** (δ_H [CD_3OD] CHOH = 5.3). Treatment of **24** with amines either directly, or after attempted formation of an acyl chloride[47] (in fact $SOCl_2$ gives **26**) gave only ring-closed products **25** and **27** (Scheme 6).

An alternative starting point is the cheap, but sparingly soluble, naphthalic anhydride **28**. Reduction with $NaBH_4$ in THF yields the lactone **29**,[48] which could be opened with lithium diethylamide (but not LDA) to form the alcohol **30** in moderate yield (Scheme 7). In principle, oxidation would give **21**, but we found that the route via the Polonovski reaction (Scheme 5) was preferable.



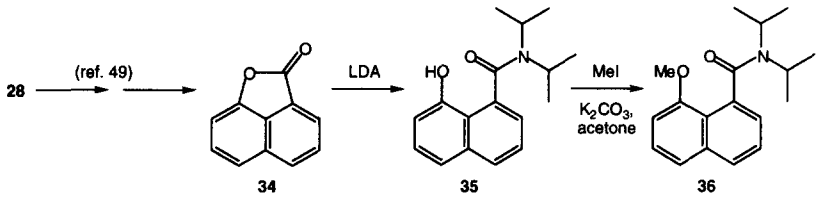
Scheme 7: Reduction of naphthalic anhydride

Direct opening of the parent anhydride **28** was a better reaction (Scheme 8). The ammonium salt **31** formed in good yield on refluxing **28** in Et_2NH, but attempts to liberate the free acid or convert it to any derivatives simply caused re-cyclisation to **28**. The more easily handled acid **32** was available from treatment of the anhydride with LDA, followed by acidification with acetic acid (strong acid again caused the re-cyclisation of **32** to **28**). **32** could be esterified with diazomethane, or via an unstable acyl chloride to give **33**. Further reactions of these compounds **31** and **32** were frustrated both by the amide's willingness to participate in any reaction involving an electrophilic intermediate at the 8-position (undesired cyclisations to **27** or **28** were common) and by the unwillingness of peri-substituted trigonal substituents to become tetrahedral (for example, it proved impossible to reduce the ester **33** to the alcohol).



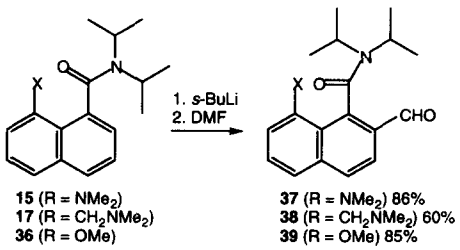
Scheme 8: Ring opening of naphthalic anhydride

8-Hydroxy and -alkoxy substituents were easily introduced by a known[49] route (Scheme 9) from the same anhydride. Lactone **34** could be made on a large scale and opened with LDA to give the 8-hydroxy compound **35**. This was methylated in high yield to give **36**.[50]



Scheme 9: Peri-methoxy substituents from naphthalic anhydride

We were initially concerned that the 8-substituted amides **3** would be resistant to ortholithiation because the 8-substituent would hinder the rotation of the amide about the Ar–CO bond necessary for the basic amide oxygen to deliver the BuLi to the *ortho* position.[51] However , there were no problems with this reaction, and **15**, **17** and **36**, were lithiated with *s*-BuLi and the organolithiums quenched with DMF[5] to give **37**, **38** and **39** (Scheme 10).



Scheme 10: Ortholithiation of 8-substituted-1-naphthamides

Conclusion

8-Substituted naphthamides may be made by perilithiation followed by trapping with a carbamyl chloride, but cannot be made by perilithiation of a naphthamide. Carbonyl-based substituents at the 8-position are best introduced by perilithiation and oxidation of dimethylaminomethyl-substituted naphthalenes: routes to these compounds from naphthalic anhydride are less successful. 8-Heterosubstituents can be made by a multi-step (but high yielding and easily scaled up) route from naphthalic anhydride, but the ability of an NMe_2 substituent to direct perilithiation makes the lithiation route more attractive in this case.

Acknowledgements

We are grateful to the EPSRC, and to Roche Discovery (Welwyn) and Zeneca Pharmaceuticals for CASE awards (to NW and CMcC). We are also grateful to Prof V. Snieckus for helpful correspondence.

Experimental

Flash chromatography refers to chromatography carried out on silica by the method of Still, Kahn and Mitra.[52] 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 15.0ml/min. Detection was at 280 nm using a Gilson 115 UV Detector. Ether refers to diethyl ether; petroleum ether to the fraction boiling between 40 °C and 60 °C. *J* values are in Hz.

2-Deuterio-N,N-diisopropyl-1-naphthamide **8**. —*sec*-Butyllithium (2.54 ml, 3.31 mmol; 1.3 M solution in hexanes) was added to a stirred solution of *N,N*-diisopropyl-1-naphthamide **1**[7] (703 mg, 2.76 mmol) in THF (40 ml) at –78 °C under an atmosphere of nitrogen. After 30 minutes, deuterium oxide (2 ml) was added to the yellow solution and the mixture was allowed to warm to ambient temperature and concentrated under reduced pressure. The aqueous residue was extracted with dichloromethane (4 × 20 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford *naphthamide* **8** (657 mg, 93%) as a white solid (>98% D by ^1H NMR) that required no further purification, m.p. 172-174 °C; ν_{max}/cm^{-1} 3054, 2992, 2965, 2930, 2359, 2340, 1621; δ_H(300MHz, $CDCl_3$) 7.94-7.83 (3H, m, ArH), 7.58-7.46 (3H, m, ArH), 3.74-3.57 (2H, m, 2 ×NCH), 1.77 (3H, d, *J* 6.9, CH_3), 1.70 (3H, d, *J* 6.7, CH_3), 1.12 (3H, d, *J* 6.7, CH_3), and 1.07 (3H, d, *J* 6.7, CH_3); δ_C(75 MHz, $CDCl_3$) 170.0, 136.6, 133.5, 129.5, 128.2, 128.1, 126.6, 126.2, 125.1, 124.8, 51.0, 45.9, 20.8, 20.7, 20.6 and 20.6; *m/z* (CI) 257 (100%, $M+H^+$) and 156 (4%, M–N*i*-Pr_2); *m/z* (EI) 256 (9%, $M+H^+$) and 156 (100%, M–N*i*-Pr_2). (Found: C, 80.11; H, 8.59; N, 5.44%. $C_{17}H_{20}NOD$ requires C, 79.7; H, 8.6; N, 5.5%).

N,N-Diethylanthracene-9-carboxamide **9**. —Oxalyl chloride (3.1 ml, 35 mmol) was added dropwise to a yellow suspension of 9-anthracenecarboxylic acid (7.017 g, 31.6 mmol) in dry dichloromethane (60 ml) and DMF (0.5 ml) at 0 °C under nitrogen. The resulting yellow mixture was stirred for 1 h at 0 °C and 1 h at 20 °C. During this time it became a clear brown solution. The solution was added to a solution of diethylamine (13.1 ml, 127 mmol) in dichloromethane (60 ml). The mixture was stirred for 4 h, diluted with CH_2Cl_2, washed with 1.5% aqueous hydrochloric acid (2 × 100 ml) and water and dried ($MgSO_4$). The solvent was removed under reduced pressure to give a crude brown solid which was recrystallised from EtOAc to yield the *amide* **9** (5.79 g, 66%) as yellow prisms, m.p. 189-192 °C; δ_H(200 MHz, $CDCl_3$) 8.45 (1 H, s, 10-ArH), 8.05-7.85 (4 H, m, ArH), 7.6-7.4 (4 H, m, ArH), 3.85 (2 H, q, *J* 7, NCH_2), 3.05 (2 H, q, *J* 7, NCH_2), 1.51 (3 H, t, *J* 7, CH_3) and 0.85 (3 H, t, *J* 7, CH_3); δ_C(200 MHz, $CDCl_3$) 169.6, 131.6, 131.3, 128.6, 127.6, 127.4, 126.6, 125.5, 125.0, 43.2, 39.1, 14.3 and 13.2; *m/z* (CI) 306 (30%, $M+H^+$) and 102 (100%). (Found: M^+, 305.1777. $C_{21}H_{23}NO$ requires *M*, 305.1780).

N,N-Diisopropyl-2-deuterio-2-(1-methylpropyl)-1,2-dihydro-1-naphthalenecarboxamide **10**. —*sec*-Butyllithium (0.60 ml of a 1.3 M solution in hexanes, 0.78 mmol) was added to a solution of naphthamide **8** (166 mg,

0.65 mmol) in THF (10 ml) at –78 °C under an atmosphere of nitrogen. After 70 minutes saturated aqueous ammonium chloride (5 ml) was added and the mixture was allowed to warm to ambient temperature. The THF was removed under reduced pressure and the aqueous residue was extracted with diethyl ether (50 ml). The organic phase was washed with water (4 ×20 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the crude product. Purification by flash chromatography on silica gel (4:1 petroleum ether–EtOAc) afforded a mixture of diastereoisomers (ca. 1^a: 5^b: 5^c: 12^d by ^{1}H NMR) of the *amide* **10** (157 mg, 77%) as a colourless oil, R_f 0.66 (2:1 petroleum ether–EtOAc); υ_{max}(film)/cm^{-1} 3028, 2959, 2926, 2873, 1650; δ_H(300 MHz, $CDCl_3$) 7.12-6.90 (4H, m, ArH), 6.48 (1H, d, *J* 9.9, C*H*=CHCH^b), 6.41 (1H, d, *J* 9.8, C*H*=CHCH^a), 6.39 (1H, d, *J* 9.9, C*H*=CHCH^d), 6.38 (1H, d, *J* 9.8, C*H*=CHCH^c), 5.91 (1H, d, *J* 9.8, CH=C*H*CH^a), 5.83 (1H, d, *J* 9.8, CH=C*H*CH^b), 5.82 (1H, d, *J* 9.8, CH=C*H*CH^c), 5.80 (1H, d, *J* 9.8, CH=C*H*CH^d), 3.98 (2H, m, NCH and C*H*CON^{i}Pr$_2$), 3.38 (1H, septet, *J* 6.7, NCH), and 1.50-1.60 (20H, m, N(CH(C*H*$_3$)$_2$)$_2$ and C*H*(C*H*$_3$)C*H*$_2$C*H*$_3$); δ_C(75 MHz, $CDCl_3$) 172.4, 133.7, 133.6, 129.8, 129.2, 127.4, 127.2, 127.0, 126.8, 126.1, 126.0, 125.9, 125.8, 49.0, 48.9, 46.2, 46.1, 45.7, 36.6, 36.0, 29.6, 27.7, 24.8, 21.1, 21.1, 21.0, 20.8, 20.7, 20.5, 17.1, 15.4, 12.4 and 12.1; *m/z* (CI) 315 (100%, M+H$^+$); *m/z* (EI) 314 (0.2%, M$^+$) and 49 (100%). (Found: M$^+$, 314.2466. $C_{21}H_{30}NO$ requires *M*, 314.2468).

Also obtained were recovered naphthamides **8** and **1** (33 mg, 20%; ratio 1.1:1 by 1H NMR)

(1R,2R*)-* and *(1R*,2S*)-N,N-Diisopropyl-2-butyl-2-deuterio-1,2-dihydro-1-naphthalenecarboxamide* **12a** (E = H) and **12b** (E = H). —*n*-Butyllithium (2.97 ml of a 1.6 M solution in hexanes, 4.75 mmol) was added dropwise to a solution of naphthamide **8** (405 mg, 1.58 mmol) and HMPA (3.30 ml, 19 mmol, 12 equiv.) in THF (14 ml) at –50 °C. The deep red-brown solution was stirred for 40 hours. Saturated aqueous ammonium chloride (5 ml) was added and the mixture was allowed to warm to ambient temperature. Water (20 ml) and diethylether (20 ml) were added, the layers were separated, and the ethereal layer was washed with water (5 × 10 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude product. Purification by flash chromatography (1:1 petroleum ether–EtOAc) gave the *amides* **12** (E = H) 205 mg (41%) as a 4.8:1 mixture of diastereoisomers **12a** and **12b** (by NMR). Preparative HPLC (25:1 hexane–EtOAc) gave *(1R*,2R*)-N,N-Diisopropyl-2-deuterio-2-butyl-1,2-dihydro-1-naphthalenecaboxamide* **12a** (E = H) as a colourless oil, t_R 9.12 min (25:1 hexane–EtOAc); ν_{max}/cm^{-1} 3000, 2962, 2871, 1642; δ_H(300 MHz, $CDCl_3$) 7.27-7.16 (3H, m, ArH), 7.08 (1H, m, ArH), 6.48 (1H, d, *J* 9.6, C*H*=CHCD), 6.09 (1H, d, *J* 9.8, CH=C*H*CD), 4.27 (1H, m, NCH), 4.23 (1H, s, C*H*CON*i*-Pr$_2$), 3.55 (1H, m, NCH), 1.69 (1H, m, C*H*$_A$H$_B$(CH$_2$)$_2$CH$_3$), 1.47 (6H, d, *J* 6.7, 2 ×NCHC*H*$_3$), 1.29 (6H, d, *J* 6.7, 2 ×NCHC*H*$_3$), 1.5-1.25 (5H, m, CH$_A$*H*$_B$(CH$_2$)$_2$CH$_3$) and 0.90 (3H, t, *J* 6.9, CH$_2$C*H*$_3$); δ_C(75 MHz, $CDCl_3$) 170.7, 134.1, 133.9, 131.7, 127.5, 127.0, 126.6, 126.5, 126.3, 48.6, 46.1, 45.2, 29.8, 29.6, 29.5, 22.8, 21.4, 21.3, 20.8, 20.7 and 14.0; m/z (CI) 315 (100%, M+H$^+$); m/z (EI) 314 (6%, M$^+$) and 49 (100%). (Found: M$^+$, 314.2474. $C_{21}H_{30}NOD$ requires M, 314.2468).

Also obtained was *(1R*,2S*)-N,N-diisopropyl-2-butyl-2-deuterio-1,2-dihydro-1-naphthalenecaboxamide* **12b** (E = H) as a colourless oil, t_R 11.5 min (25:1 hexane–EtOAc); ν_{max}/cm^{-1} 3060, 3021, 2998, 2962, 2929, 2870, 2861, 1642; δ_H(300 MHz, $CDCl_3$) 7.18 (2H, m, ArH), 7.09 (1H, m, ArH), 7.03 (1H, m, ArH), 6.48 (1H, d, *J* 9.8, C*H*=CHCD), 6.01 (1H, d, *J* 9.8, CH=C*H*CD), 4.08 (1H, septet, *J* 6.7, NCH), 3.86 (1H, s, C*H*CON*i*-Pr_2), 3.61 (1H, bm, NCH), 1.61 (3H, d, *J* 6.9, NCHCH_3), 1.53 (3H, d, *J* 6.7, NCHCH_3), 1.6-1.3 (6H, m, $(CH_2)_3$), 1.32 (3H, d, *J* 6.6, NCHCH_3), 1.20 (3H, d, *J* 6.7, NCHCH_3) and 0.96 (3H, t, *J* 7.0, CH_2CH_3); δ_C(75 MHz, $CDCl_3$) 172.4, 133.8, 133.7, 132.7, 127.2, 126.9, 126.5, 125.9, 125.6, 48.8, 48.4, 46.2, 32.6, 28.4, 22.8, 21.2, 20.9, 20.5 and 13.9; m/z (CI) 315 (100%, M+H+); m/z (EI) 314 (4%, M+), 186 (4%, M-CON*i*-Pr_2), 128 (6%, CON*i*-Pr_2) and 86 (100%). (Found: M+, 314.2471. $C_{21}H_{30}NOD$ requires M, 314.2468).

Also obtained were recovered naphthamides **8** and **1** (190 mg, 47%, ratio 1.1:1 by mass spectrometry) as a white solid.

The method was repeated with **1** (493 mg, 1.9 mmol) in the place of **8**. A 1:4 mixture of *de-deuterio*-**12a** (E = H) and *de-deuterio*-**12b** (E = H) was obtained (121 mg, 20%), which were separated by preparative HPLC to yield *(1R*,2R*)-Diisopropyl-2-butyl-1,2-dihydro-1-naphthalenecaboxamide de-deuterio*-**12a** (E = H); δ_H(300 MHz, $CDCl_3$) 7.27-7.15 (3H, m, ArH), 7.09 (1H, m, ArH), 6.48 (1H, d, *J* 9.8, C*H*=CHCH), 6.09 (1H, dd, *J* 9.6 and 4.7, CH=C*H*CH), 4.27 (1H, m, NCH), 4.23 (1H, s, C*H*CON*i*-Pr_2), 3.55 (1H, m, NCH), 2.63 (1 H, m, C*H*CH_2) 1.70 (1H, m, $CH_AH_B(CH_2)_2CH_3$), 1.47 (6H, d, *J* 6.7, 2 × NCHCH_3), 1.28 (6H, d, *J* 6.7, 2 × NCHCH_3), 1.5-1.25 (5H, m, $CH_AH_B(CH_2)_2CH_3$) and 0.91 (3H, t, *J* 6.9, CH_2CH_3); δ_C(75 MHz, $CDCl_3$) 170.7, 134.1, 133.9, 131.8, 127.5, 127.0, 126.7, 126.5, 126.4, 48.7, 46.1, 45.2, 37.0, 29.9, 29.5, 22.8, 21.4, 21.3, 20.8, 20.7 and 14.0; m/z (CI) 314 (100%, $M+H^+$); m/z (EI) 313 (9%, M^+) and 128 (49%, CON*i*-Pr_2) (Found: M^+, 313.2400. $C_{21}H_{31}NO$ requires M, 313.2406). Irradiation of the peak at 2.63 gave a 7.5% enhancement of the peak at 4.23.

Also obtained was *(1R*,2S*)-N,N-Diisopropyl-2-butyl-2-1,2-dihydro-1-naphthalenecaboxamide de-deuterio*-**12b** (E = H) as a colourless oil; δ_H(300 MHz, $CDCl_3$) 7.18 (2H, m, ArH), 7.09 (1H, m, ArH), 7.03 (1H, m, ArH), 6.49 (1H, dd, *J* 9.8 and 2.6, C*H*=CHCH), 6.02 (1H, dd, *J* 9.8 and 2.3, CH=C*H*CH), 4.09 (1H, septet, *J* 6.7, NCH), 3.87 (1H, d, *J* 13.2, C*H*CON*i*-Pr_2), 3.62 (1H, bm, NCH), 3.03 (1 H, m, C*H*CH_2), 1.62 (3H, d, *J* 6.7, NCHCH_3), 1.53 (3H, d, *J* 6.7, NCHCH_3), 1.6-1.3 (6H, m, $(CH_2)_3$), 1.32 (3H, d, *J* 6.6, NCHCH_3), 1.21 (3H, d, *J* 6.7, NCHCH_3) and 0.96 (3H, t, *J* 7.0, CH_2CH_3); δ_C(75 MHz, $CDCl_3$) 172.4, 133.8, 133.7, 132.8, 127.2, 126.9, 126.5, 125.9, 125.6, 48.8, 48.5, 46.2, 37.7, 32.7, 28.4, 22.8, 21.2, 20.9, 20.5 and 13.9; m/z (CI) 315 (100%, M+H+); m/z (EI) 313 (3%, M^+), 185 (7%, M-CON^iPr_2), 128 (11%, CON*i*-Pr_2) and 86 (100%). (Found: M^+, 314.2412. $C_{21}H_{31}NO$ requires M, 314.2406).

Also obtained was recovered naphthamide **1** (237 mg, 48%) as a white solid.

(1S,2S*)-N,N-Diisopropyl-2-butyl-2-deuterio-1-methyl-1,2-dihydro-1-naphthalenecarboxamide* **12a** (E = Me). —*n*-Butyllithium (2.75 ml of a 1.6 M solution in hexanes, 4.40 mmol) was added dropwise to a solution of naphthamide **8** (375 mg, 1.47 mmol) and HMPA (0.76 ml, 4.40 mmol) in THF (20 ml) at –50 °C. The deep red-

brown solution was stirred for 24 hours. Methyl iodide (0.50 ml, 8.03 mmol) was added and after a further 30 minutes the mixture was allowed to warm to ambient temperature. After 2 hours saturated aqueous ammonium chloride (10 ml) was added and the THF was removed under reduced pressure. Diethylether (20 ml) was added, the layers were separated, and the ethereal layer was washed with water (5 × 10 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude product. Purification by flash chromatography (15:1 petroleum ether–EtOAc) gave the *amide* **12a** (E = Me) (293 mg, 61%) as a colourless oil that crystallised on standing, m.p. 68-69 °C; R_f 0.48 (5:1 petroleum ether–EtOAc); λ_{max}/nm (ε_{max}) (CH_2Cl_2) 232 (15090) 276 (7205); υ_{max}/cm^{-1} 3057, 2995, 2962, 2929, 2863, 1631; δ_H(300 MHz, $CDCl_3$) 7.15-6.95 (4H, m, ArH), 6.37 (1H, d, *J* 10.0, C*H*=CHCD), 5.91 (1H, d, *J* 10.0, CH=C*H*CD), 3.79 (1H, septet, *J* 6.5, NCH), 3.17 (1H, septet, *J* 6.7, NCH), 1.55 (3H, s, CH_3), 1.70-1.23 (6H, m, $CH_2CH_2CH_2$), 1.40 (3H, d, *J* 6.7, NCHCH_3), 1.32 (3H, d, *J* 6.7, NCHCH_3), 0.98 (3H, d, *J* 6.5, NCHCH_3), 0.90 (3H, t, *J* 7.0, CH_2CH_3) and 0.01 (3H, d, *J* 6.5, NCHCH_3); δ_C(75 MHz, $CDCl_3$) 173.1, 139.2, 131.1, 129.5, 127.7, 127.3, 127.2, 126.4, 125.6, 49.2, 47.1, 46.1, 44.7, 36.4, 30.9, 30.1, 22.6, 20.9, 20.4, 19.6, 18.1 and 13.9; *m/z* (CI) 329 (100%, M+H$^+$); *m/z* (EI) 328 (4%, M$^+$), 128 (62%, M-CON*i*-Pr_2) and 86 (100%). (Found C, 80.74; H, 10.14; N, 4.01%; $C_{22}H_{32}NOD$ requires C, 80.4; H, 10.1; N, 4.3%).

Also obtained was a mixture of the diastereoisomers of **12a** (E = H) (32 mg, 7%) and some recovered starting material **8** and **1** (120 mg, 32%) (ratio of 1.1:1 by MS).

(1S,2S*)-N,N-Diisopropyl-2-butyl-2-deuterio-1-propyl-1,2-dihydro-1-naphthalenecarboxamide* **12a** (E = *n*-Pr). —In the same way, *n*-butyllithium (1.97 ml of a 1.6 M solution in hexanes, 3.15 mmol), naphthamide **8** (269 mg, 1.05 mmol), HMPA (0.55 ml, 3.15 mmol), THF (15 ml) and 1-iodopropane gave, after 28 h at –50 °C and 60 min at 20 °C, a crude product which was purified by flash chromatography (15:1 petroleum ether–EtOAc) to yield the amide **12a** (E = *n*-Pr) (195 mg, 52%) as a colourless oil that crystallised on standing, R_f 0.52 (5:1 petroleum ether–EtOAc); υ_{max}/cm^{-1} 3026, 3015, 2959, 2930, 2870, 1629; δ_H(300 MHz, $CDCl_3$) 7.18-6.98 (4H, m, ArH), 6.38 (1H, d, *J* 10.0, C*H*=CHCD), 5.97 (1H, d, *J* 10.0, CH=C*H*CD), 3.76 (1H, septet, *J* 6.5, NCH), 3.21 (1H, septet, *J* 6.7, NCH), 2.20 (1H, dt, *J* 13.5 and 4.5, $CH_AH_BCH_2CH_3$ (propyl chain)), 1.76 (1H, m, $CH_AH_BCH_2CH_3$ (propyl chain)), 1.68-1.26 (6H, m, $(CH_2)_3CH_3$), 1.44 (3H, d, *J* 6.7, NCHCH_3), 1.36 (3H, d, *J* 6.7, NCHCH_3), 1.04 (3H, d, *J* 6.5, NCHCH_3), 0.94 (3H, t, *J* 6.9, $(CH_2)_3CH_3$), 0.83 (3H, t, *J* 7.3, $CH_2CH_2CH_3$ (propyl chain)) and 0.01 (3H, d, *J* 6.5, NCHCH_3); δ_C(75 MHz, $CDCl_3$) 173.8, 137.3, 132.1, 130.0, 127.6, 127.2, 126.9, 126.2, 125.5, 52.2, 48.4, 46.9, 46.1, 31.5, 30.3, 22.7, 21.1, 20.4, 19.6, 18.0, 17.6, 14.6 and 13.9; *m/z* (CI) 357 (9%, M+H$^+$) and 315 (100%); *m/z* (EI) 356 (1%, M$^+$) and 128 (100%, CON^{i}Pr$_2$). (Found M$^+$, 356.2946. $C_{24}H_{36}NOD$ requires *M*, 356.2938).

Also obtained was *N,N-Diisopropyl-2-propyl-1-naphthamide* **13** (35 mg, 11%) as a white solid, m.p. 120-121 °C; υ_{max}/cm^{-1} 3053, 2961, 2931, 2871, 1618; δ_H(300 MHz, $CDCl_3$) 7.81 (3H, m, ArH), 7.49 (2H, m, ArH), 7.40 (1H, d, *J* 8.5, ArH), 3.60 (2H, m, 2 × NCH), 2.80 (1H, m, $CH_AH_BCH_2CH_3$), 2.68 (1H, m,

$CH_AH_BCH_2CH_3$), 1.85 (2H, m, $CH_2CH_2CH_3$), 1.82 (3H, d, *J* 6.9, $NCHCH_3$), 1.73 (3H, d, *J* 6.7, $NCHCH_3$), 1.12 (3H, d, *J* 6.6, $NCHCH_3$), 1.05 (3H, t, *J* 7.3, CH_2CH_3) and 1.02 (3H, d, *J* 6.2, $NCHCH_3$); δ_C(75 MHz, $CDCl_3$) 169.5, 135.3, 131.8, 129.7, 128.2, 127.8, 127.6, 127.1, 126.3, 125.3, 124.8, 50.9, 46.0, 35.5, 24.1, 21.1, 20.8, 20.6, 20.4 and 14.3; *m/z* (CI) 298 (100%, M+H$^+$) and 197 (5%, M–N*i*-Pr$_2$); *m/z* (EI) 297 (9%, M$^+$). (Found M$^+$, 297.2090. $C_{20}H_{27}NO$ requires *M*, 297.2093).

Also obtained was **12** (E = H) (63 mg, 19%) as a mixture of diastereoisomers, along with recovered naphthamides **8** and **1** (48 mg, 18%; 0.8:1 by MS).

Attempted lithiation of anthracenecarboxamide **9**. –*sec*-Butyllithium (1.2 ml of a 1.3 M solution in hexanes, 1.5 mmol) was added to a solution of **9** (277 mg, 1.0 mmol) in THF (20 ml) at –78 °C. After 1 h, methyl iodide (1 ml) was added to the green solution. Stirring was continued for 10 min at –78 °C, and the mixture was allowed to warm to –20 °C. Water and dichloromethane were added to the yellow solution, the layers were separated and the aqueous layer was extracted with dichloromethane (20 ml ×2). The combined organic fractions were washed with water, dried ($MgSO_4$) and evaporated to give a crude product *m/z* (CI) 350 [**14** (E = Me) + H$^+$] and 336 [**14** (E = H) + H$^+$].

N,N-Dimethylaminomethylnaphthalene **4** (X = CH_2NMe_2).[20] —By the method of Gay and Hauser,[20] a solution of 1-chloromethylnaphthalene (73 g, 0.41 mol) and anhydrous methylamine (80 g, 1.77 mol) in absolute ethanol (600 ml) was stirred in a tightly stoppered flask for 1 week at ambient temperature. The solvent was removed and the residue stirred with excess aqueous 6 M sodium hydroxide (100 ml) and ether (150 ml). The layers were separated and the alkaline aqueous layer extracted with ether (3 ×50 ml). The combined ethereal extracts were extracted with aqueous 3 M hydrochloric acid (4 × 70 ml), and the combined acidic extracts were made strongly alkaline with solid sodium hydroxide. The resulting solution was the extracted with diethylether (4 × 70 ml) and the combined ethereal extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude product as a brown oil. Distillation by Kugelrohr under reduced pressure afforded the pure amine **4** (X = CH_2NMe_2)[20] (40 g, 52%) as a colourless oil, b.p. 98-103 °C, 0.5 mmHg (lit.,[20] 148-152 °C, 16mmHg).

N,N-Diisopropyl-8-(dimethylamino)-naphthamide **15**. —By a modification of the method of Gay and Hauser[19],*tert*-butyllithium (7.7 ml of a 1.7 M solution in hexane, 13 mmol) was added dropwise to a stirred solution of *N,N*-dimethylaminonaphthalene **4** (X = CH_2NMe_2) (2g, 12 mmol) in dry pentane (50 ml) under nitrogen at ambient temperature. After 24 h, the mixture was cooled to 0 °C and was added dropwise by cannula over 30 min to a solution of diisopropylcarbamyl chloride (4 g, 24 mmol) in dry pentane (50 ml). The mixture was stirred at ambient temperature for 5 h, poured into water and extracted with ether. The extracts were washed with aqueous HCl (1M) and with brine, dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was recrystallised from petroleum ether to give the *amide* **15** (2.7 g, 75%) as white prisms, m.p. 89-

91°C; R_f 0.27 (7:1 petroleum ether–EtOAc); ν_{max} (film)/cm^{-1} 2964 and 1630; δ_H(300MHz, $CDCl_3$) 7.80 (1H, d, *J* 8, $ArH^{2)}$, 7.62 (1H, d, *J* 8, ArH^4), 7.48 (1H, t, *J* 8, ArH^3), 7.44 (1H, t, *J* 8, ArH^6), 7.34 (1H, d, *J* 8, ArH^7), 7.30 (1H, d, *J* 8, ArH^5), 3.50 (1H, septet, *J* 7, CHN), 3.22 (1H, septet, *J* 7, CHN), 2.80 (3H, s, NCH_3), 2.60 (3H, s, NCH_3), 1.70 (3H, d, *J* 7, $NCHCH_3$), 1.60 (3H, d, *J* 7, $NHCH_3$), 1.00 (3H, d, *J* 7, $NCHCH_3$) and 0.90 (3H, d, *J* 7, $NCHCH_3$), δ_C(75MHz; $CDCl_3$) 171.1 (N-C=O), 151.9, 135.3, 135.2, 128.4, 127.0, 126.0, 125.4, 125.1, 124.9, 117.9 (Ar C), 49.8, 49.7 ($N(CH_3)_2$), 45.2, 44.8 ($N(CH)_2$), 20.6, 20.5, 20.5 and 19.7 (CH_3 ×4). (Found: M$^+$, 298.2041, C, 76.62; H, 8.89; N, 9.44%. $C_{19}H_{26}N_2O$ requires *M*, 298.2045, C, 76.76; H 8.75; N 9.43%).

On one occasion, the order of addition was reversed, and the carbamyl chloride (14.3 g, 88 mmol) was added to the lithiated amine [made from amine **4** (10 g, 58 mmol) and *n*-butyllithium (52 ml of 1 a.7 M solution in hexanes, 88 mmol)]. Recrystallisation of the crude product gave a single diastereoisomer of *(1R*,2R*,aS*)-N,N-Diisopropyl-2-(1'-N,N-diisopropylaminocarbonyl-8'-dimethylaminonaphth-2'-yl)-8-dimethylamino-1,2-dihydronaphthalene-1-carboxamide* **18** (4.4 g, 13%) as a white solid, R_f 0.32 (6:1 petroleum ether–EtOAc); ν_{max} (film)/cm^{-1} 2963 and 1630; δ_H(300MHz, $CDCl_3$) 7.5-7.0 (8H, m, ArH), 6.60 (1H, d, *J* 9.5, *H*C=C), 6.03 (1H, dd, *J* 6, 9.5, C=C*H*), 4.72 (1H, s, *H*CCON*i*-Pr_2), 4.44 (1H, d, *J* 6, CH=CHC*H*), 3.4 (4H, m, $NCH(CH_3)_2$ × 4), 2.8 (3H, s, NMe), 2.54 (3H, s, NMe), 2.32 (6H, s, NMe_2), 1.64 (3H, d, *J* 7), 1.62 (3H, d, *J* 7), 1.42 (3H, d, *J* 7), 1.25 (6H, m), 0.94 (3H, d, *J* 7), 0.90 (3H, d, *J* 7) and 0.75 (3H, d, *J* 7) ($CH(CH_3)_2$ × 4); δ_C(75MHz; $CDCl_3$) 171.5, 168.6 (C=O), 152.0, 138.2, 136.2, 133.9, 131.0, 122.9, 119.8, 115.7 (Ar and CH=CH), 50.5, 49.3, 48.8, 45.7, 45.6, 45.2, 43.3, 42.9, 38.7, 21.5, 20.9, 20.8, 20.6, 20.5, 20.4 and 19.9; *m/z* (CI) 597 (100%, M$^+$). (Found: M$^+$, 596.4091. $C_{38}H_{52}N_4O_2$ requires *M*, 596.4090.)

N,N-Diethyl-8-[(dimethylamino)methyl]-1-naphthamide **16**. —Following the method of Gay and Hauser,[20] *n*-Butyllithium (24.0 ml of a 1.6 M solution in hexanes, 38.38 mmol) was added to a solution of amine **4** (X = CH_2NMe_2) (6.396 g, 34.58 mmol) in diethyl ether (110 ml) at 0 °C under an atmosphere of nitrogen. The resulting red solution was stirred for 24 hours at ambient temperature and added via a cannula to a stirred solution of diethylcarbamyl chloride (5.26 ml, 41.50 mmol) in diethyl ether (60 ml). After 1 h, water (30 ml) was added and the mixture was stirred for a further 1 h. The mixture was washed successively with saturated aqueous sodium hydrogen carbonate (30 ml) and brine (30 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude product as a brown oil. Kugelrohr distillation under reduced pressure afforded the *amide* **16** (5.991 g, 61%) as a brown oil, (bp 250 °C, 1.0 mmHg); υ_{max} (film)/cm^{-1} 2973, 2938, 2870, 2858, 2815, 2766, 1630; δ_H(300 MHz, $CDCl_3$) 7.95-7.75 (3H, m, ArH), 7.50 (2H, m, ArH), 7.37 (1H, dd, *J* 8.5 and 1.5, ArH), 4.14 (1H, d, *J* 14.0, $(CH_3)_2NCH_AH_B$), 3.87 (1H, d, *J* 14.0, $(CH_3)_2NCH_AH_B$), 3.72 (2H, m, $CH_AH_BCH_3$), 3.63 (2H, m, $CH_AH_BCH_3$), 1.39 (3H, t, *J* 7.5, CH_2CH_3) and 1.07 (3H, t, *J* 7.5, CH_2CH_3); δ_C(75 MHz, $CDCl_3$) 172.9, 135.0, 133.9, 130.5, 129.2, 129.1, 128.2, 126.2, 126.0, 124.4, 61.3, 45.1, 44.1, 39.6, 13.5 and 12.8; *m/z* (CI) 285 (100%, M+H$^+$). (Found: M+H$^+$, 285.1965. $C_{18}H_{24}N_2O$ requires *M*+H, 285.1967).

N,N-Diisopropyl-8-[(dimethylamino)methyl]-1-naphthamide **17**. —In the same way, *n*-butyllithium (5.63 ml of a 1.6 M solution in hexanes, 9.00 mmol), amine **4** (1.5 g, 8.11 mmol) in diethylether (50 ml) and diisopropylcarbamyl chloride (1.47 g, 9.73 mmol) in diethyl ether (30 ml) gave a crude product which was triturated with petroleum ether to afford the *amide* **17** (1.6 g, 63%) as pale brown blades, m.p. 146-149 °C; λ_{max}, nm (ε_{max}) (CH_2Cl_2) 232 (40450) 292 (7217); υ_{max} (film)/cm^{-1} 2971, 2938, 2817, 2768, 1629; δ_H(300 MHz, $CDCl_3$) 8.00 (1H, d, *J* 7.0, ArH), 7.90 (1H, d, *J* 8.2, ArH), 7.81 (1H, d, *J* 8.0, ArH), 7.55 (1H, t, *J* 7.6, ArH), 7.46 (1H, t, *J* 7.3, ArH), 7.30 (1H, d, *J* 6.9, ArH), 4.30 (1H, d, *J* 15.4, $(CH_3)_2NCH_AH_B$), 3.91 (1H, d, *J* 15.5, $(CH_3)_2NCH_AH_B$)), 3.73 (1H, septet, *J* 6.7, NCH), 3.62 (1H, septet, *J* 6.6, NCH), 2.43 (6H, s, $(CH_3)_2NCH_2$), 1.74 (3H, d, *J* 6.7, $NCHCH_3$), 1.66 (3H, d, *J* 6.7, $NCHCH_3$), 1.19 (3H, d, *J* 6.7, $NCHCH_3$), 1.13 (3H, d, *J* 6.5, $NCHCH_3$); δ_C(75 MHz, $CDCl_3$) 172.3, 134.9, 134.9, 134.5, 130.0, 128.1, 127.8, 127.0, 125.9, 124.8, 124.2, 60.8, 51.0, 45.8, 45.6, 20.3, 19.9 and 19.8; *m/z* (CI) 313 (100%, M+H$^+$) and 196 (31%); *m/z* (EI) (312 (3%, M$^+$) and 196 (100%). (Found: M$^+$, 312.2205. $C_{20}H_{28}N_2O$ requires *M*, 312.2205).

N,N-Diethyl-8-[(dimethylamino)methyl]-1-naphthamide N-oxide **19**. —A solution of naphthamide **16** (5.902 g, 20.8 mmol), dichloromethane (33 ml), ethanol (33 ml) and 30% hydrogen peroxide (6.6 ml, 58 mmol) was heated to reflux for 26 hours [until no starting was present by TLC (2:1 petroleum ether–EtOAc)]. 10% Pd/C (1.11 g) was added, and the heating continued at reflux for a further 19 hours. The mixture was filtered (Celite), concentrated under reduced pressure (water bath temperature <35 °C), and the residue was dissolved in dichloromethane (20 ml), shaken vigorously with anhydrous magnesium sulphate, filtered and concentrated under reduced pressure to afford the crude *N-oxide* **19** (2.834 g) as a brown oil, υ_{max} (film)/cm^{-1} 3417, 2971, 2934, 1619; δ_H(300 MHz, $CDCl_3$) 8.29 (1H, d, *J* 7.0, ArH), 8.00 (1H, d, *J* 7.9, ArH), 7.95 (1H, d, *J* 8.1, ArH), 7.61 (1H, t, *J* 7.7, ArH), 7.52 (1H, t, *J* 7.3, ArH), 7.38 (1H, d, *J* 7.0, ArH), 5.17 (1H, d, *J* 13.1, CCH_AH_BNO), 4.67 (1H, d, *J* 13.0, CCH_AH_BNO), 3.8-3.5 (2H, m, CH_2CH_3), 3.42 (3H, s, CH_3), 2.85 (2H, m, CH_2CH_3), 2.76 (3H, s, CH_3), 1.35 (3H, t, *J* 7.2, CH_2CH_3) and 0.85 (3H, t, *J* 7.1, CH_2CH_3); δ_C(75 MHz, $CDCl_3$) 172.7, 135.2, 134.2, 132.4, 131.8, 130.8, 128.6, 126.9, 125.9, 125.7, 124.8, 69.8, 60.2, 54.8, 43.2, 39.5, 13.6 and 12.6; *m/z* (CI) 301 (24%, M+H$^+$), 285 (39%, M-CH_3), 271 (31%, M–Et) and 74 (100%). (Found: M$^+$, 300.1831. $C_{18}H_{24}N_2O_2$ requires *M*, 300.1838).

N,N-Diisopropyl-8-[(dimethylamino)methyl]-1-naphthamide N-oxide **20**. —In the same way, the amine **17** (2.441 g, 7.82 mmol), dichloromethane (25 ml), ethanol (25 ml) and 30% hydrogen peroxide (4.8 ml, 42 mmol) gave after 48 h and after 7 h with 10% Pd/C (0.72 g) the crude *N-oxide* **21** (2.452 g) as a brown oil, *m/z* (CI) 329 (37%M+H$^+$) and 284 (100%). (Found: M$^+$, 328.2157. $C_{26}H_{28}N_2O_2$ requires *M*, 328.2151).

N,N-Diethyl-8-formyl-1-naphthamide **21**. —Trifluoroacetic anhydride (4.96 ml, 18.90 mmol) was added dropwise over 15 minutes to a solution of *N*-oxide **19** (2.834 g, 9.45 mmol) in dichloromethane (15 ml) at 0 °C

under an atmosphere of nitrogen. After 1 hour, the mixture was allowed to warm to ambient temperature. After 15 minutes, water (40 ml) was added and the mixture was stirred for a further 2 hours and extracted with dichloromethane (4 ×10 ml. The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (3 ×15 ml) and brine (15 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude product. Purification by flash chromatography on silica gel (2:1 petroleum ether–EtOAc) afforded the *aldehyde* **20** (1.012 g, 19% from **16**) as a brown oil, λ_{max}/nm (ε_{max}) (CH_2Cl_2) 234 (22500) 314 (6110); υ_{max} (film)/cm^{-1} 2974, 2936, 2875, 1688, 1626; δ_H(300 MHz, $CDCl_3$) 10.5 (1H, s, CHO), 8.12 (1H, d, *J* 7.5, ArH), 8.07 (1H, d, *J* 7.5, ArH), 8.01 (1H, dd, *J* 5.6 and 1.9, ArH), 7.60 (3H, m, ArH), 3.74 (1H, m, NCH_AH_B), 3.57 (1H, m, $NCCH_AH_B$), 3.26 (septet, *J* 7.5, 2 × NCH_AH_B), 1.36 (3H, t, *J* 7.5, CH_3) and 1.10 (3H, t, *J* 7.5, CH_3); δ_C(75 MHz, $CDCl_3$) 192.5, 172.0, 134.9, 134.4, 134.1, 133.7, 130.8, 130.3, 127.3, 127.2, 125.9, 125.6, 43.4, 39.3, 13.6 and 12.3; *m/z* (CI) 256 (100%, M+H$^+$); *m/z* (EI) 255 (2%, M$^+$), 226 (89%, M–C_2H_5), 183 (49%, M–$N(C_2H_5)_2$) and 49 (100%). (Found: M+H$^+$, 256.1347. $C_{16}H_{17}NO_2$ requires *M*+H, 256.1337).

N,N-Diisopropyl-8-formyl-1-naphthamide **22**. —In the same way, trifluoroacetic anhydride (2.11 ml, 15.0 mmol) and the *N*-oxide **21** (2.452g, 7.48 mmol)gave, after purification by flash chromatography on silica gel (2:1 petroleum ether–EtOAc), the *aldehyde* **22** (0.894 g, 40% from **17**) as a white solid, m.p. 120-122 °C (EtOAc); υ_{max} (film)/cm^{-1} 2971, 2933, 1684, 1625; δ_H(300 MHz, $CDCl_3$) 10.75 (1H, s, CHO), 8.2-7.9 (3H, m, ArH), 7.7-7.5 (3H, m, ArH), 3.75 (1H, septet, *J* 6.7, NCH), 3.61 (1H, septet, *J* 7.7, NCH), 1.69 (3H, d, *J* 6.9, CH_3), 1.64 (3H, d, *J* 6.7, CH_3), 1.14 (3H, d, *J* 6.6, CH_3), 1.13 (3H, d, *J* 6.7, CH_3); δ_C(75 MHz, $CDCl_3$) 193.1, 171.5, 134.9, 134.5, 134.0, 129.9, 129.9, 127.3, 126.3, 125.9, 125.6, 51.4, 46.3, 20.6, 20.1 and 19.6; *m/z* (CI) 284 (100%, M+H$^+$); *m/z* (EI) 283 (6%, M$^+$), 183 (47%, M-N^{i}Pr$_2$) and 49 (100%). (Found: M$^+$, 283.1571. $C_{18}H_{21}NO_2$ requires *M*, 283.1572).

3-Hydroxy-1H,3H-benzo[de]isochromen-1-one **24** (1,8-Naphthaldehydic acid).[46] —By the method of Graebe and Gfeller,[46] acenaphthaquinone (20 g, 0.11 mmol) and 30% potassium hydroxide solution were heated with constant stirring at 150 °C for 10 minutes. The mixture was diluted with water and filtered with suction. The filtrate was acidified with aqueous 3 M hydrochloric acid, and the white precipitate which formed was separated by filtration and dissolved as completely as possible in sodium bicarbonate solution. Charcoal was added, and the suspension was filtered. The filtrate was acidified and the precipitate was removed by filtration and recrystallised from toluene to give the isochromen-1-one **24** (2.589 g, 13%), m.p. 165-167 °C (lit.,[46] 167 °C).

3-(Diethylamino)-1H,3H-benzo[de]isochromen-1-one **25**. —A solution of 1,8-naphthaldehydic acid **24** (1.445 g, 7.23 mmol) in diethylamine (13 ml) was heated to 80 °C for 25 hours. The mixture was cooled and extracted with diethylether (5 ×20 ml). The combined organic extracts were washed with aqueous 1 M hydrochloric acid

(3 ×30 ml), saturated sodium hydrogen carbonate (3 ×30 ml), water (30 ml) and brine (30 ml), and dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude product which was purified by flash chromatography on silica gel (4:1 petroleum ether–EtOAc) to afford *amine* **25** (0.981 g, 53%) as a pale brown solid, m.p. 71-74 °C (EtOAc); R_f 0.33 (4:1 petroleum ether–EtOAc); υ_{max} (film)/cm^{-1} 3060, 2970, 2934, 2871, 1710; δ_H(300 MHz, $CDCl_3$) 8.48 (1H, d, *J* 7.5, ArH), 8.13 (1H, d, *J* 7.5, ArH), 7.42 (1H, d, *J* 7.5, ArH), 7.16 (3H, m, ArH), 6.75 (1H, s, C*H*NEt$_2$), 2.95 (2H, m, C*H*$_2$CH$_3$), 2.86 (2H, m, C*H*$_2$CH$_3$), 1.14 (6H, t, *J* 7.5, 2 ×CH$_3$); δ_C(75 MHz, $CDCl_3$) 165.4, 133.4, 132.1, 129.5, 129.3, 129.0, 127.9, 126.6, 126.2, 125.5, 120.5, 97.1, 42.8 and 14.0; *m/z* (CI) 256 (100%, M+H$^+$); *m/z* (EI) 255 (4%, M$^+$), 183 (M-NEt$_2$) and 127 (100%). (Found: M$^+$, 255.1258. $C_{16}H_{17}NO_2$ requires *M*, 255.1259).

3-(Diisopropylamino)-1H,3H-benzo[de]isochromen-1-one **27**. —Thionyl chloride (2.82 ml, 38.84 mmol) was added to a solution naphthaldehydic acid **24** (2.589 g, 12.95 mmol) and the mixture was heated to reflux for 2.5 hours, cooled, and diluted with dichloromethane (12 ml). Diisopropylamine (3.63 ml, 25.89 mmol) was added, and the mixture was heated to reflux for 6 hours. The reaction mixture cooled and washed with aqueous 1 M hydrochloric acid (3 × 15 ml), saturated aqueous sodium hydrogen carbonate (2 × 20 ml), water (20 ml) and brine (20 ml), and dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude product. Purification by flash chromatography on silica gel (4:1 petroleum ether–EtOAc) afforded the *amine* **27** (2.158 g, 59%) as a pale brown solid, R_f 0.33 (4:1 petroleum ether–EtOAc); υ_{max} (film)/cm^{-1} 2967, 2930, 1694; δ_H(300 MHz, $CDCl_3$) 8.48 (1H, d, *J* 7.2, ArH), 8.11 (1H, d, *J* 8.3, ArH), 7.91 (1H, m, ArH), 7.70-7.56 (3H, m, ArH), 6.89 (1H, s, C*H*N^{i}Pr$_2$), 3.30 (2H, bm, 2 ×NCH), 1.35 (6H, bm, 2 ×CH$_3$) and 1.20 (6H, m, 2 ×CH$_3$); δ_C(75 MHz, $CDCl_3$) 165.7, 133.2, 132.2, 130.9, 129.4, 127.9, 126.5, 126.2, 125.2, 120.9, 94.9, 47.3, 44.7, 23.2 and 22.7; *m/z* (CI) 284 (100%, M+H$^+$); *m/z* (EI) 283 (8%, M$^+$), 183 (88%, M-N*i*-Pr$_2$) and 196 (100%). (Found: M$^+$, 283.1572. $C_{18}H_{21}NO_2$ requires *M*, 283.1572).

1H,3H-Benzo[de]isochromen-1-one **29**.[48] —By the method of Fuson and Munn,[48] a suspension of sodium borohydride (0.237 g, 6.26 mmol) in THF (125 ml) was sonicated for 2 hours and then cooled in an ice bath. A solution of naphthalic anhydride (1.982 g, 10.00 mmol) in THF (60 ml) was added dropwise over 15 minutes and the mixture was stirred for a further 24 hours at ambient temperature and acidified to pH<2 with aqueous 6 M hydrochloric acid. After 30 minutes, water (50 ml) was added and the mixture was stirred for a further 2.5 hours. The THF was removed under reduced pressure and the aqueous residue was extracted with diethylether (4 ×50 ml). The combined ethereal extracts were washed with brine and dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the crude product. Purification by flash column chromatography on silica gel (4:1 petroleum ether–EtOAc) afforded the lactone **29** as a pale yellow solid (0.810 g, 44%), m.p. 159-160 °C (lit.,[48] 156-157 °C).

[8-[(Diethylamino)methyl]-1-naphthyl]methanol **30**. — *n*-Butyllithium (1.88 ml of a 1.6 M solution in hexanes, 3.00 mmol) was added to a solution of diethylamine (0.28 ml, 2.73 mmol) in THF (5 ml) at 0 °C under an atmosphere of nitrogen. After 30 min, a solution of lactone **29** (360 mg, 1.96 mmol) in THF (5 ml) was added. The deep purple solution was stirred for 1 hour. Saturated aqueous ammonium chloride (5 ml) was added, and the mixture was extracted with diethylether (5 × 15 ml) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude product. Purification by flash chromatography on silica gel (2:1 petroleum ether–EtOAc) afforded the *amide* **30** (315 mg, 45%) as a pale yellow oil, υ_{max} (film)/cm^{-1} 3422, 2975, 2936, 1723, 1605; δ_H(300 MHz, $CDCl_3$) 7.95 (1H, dd, *J* 8.1 and 1.2, ArH), 7.88 (1H, dd, *J* 8.1 and 2.1, ArH), 7.64 (1H, dd, *J* 7.2 and 1.5, ArH), 7.52 (2H, m, ArH), 7.37 (1H, dd, *J* 6.9 and 1.5, ArH), 5.12 (1H, d, *J* 13.2, CH_AH_BOH), 4.65 (1H, d, *J* 13.2, CH_AH_BOH), 3.85 (1H, m, $CH_AH_BCH_3$), 3.64 (1H, m, $CH_AH_BCH_3$), 3.27 (2H, q, *J* 6.9, CH_2CH_3), 1.43 (3H, t, *J* 7.2, CH_2CH_3) and 1.12 (3H, t, J 7.2, CH_2CH_3); δ_C(75 MHz, $CDCl_3$) 174.1, 136.9, 135.1, 132.9, 130.6, 129.5, 128.1, 126.2, 125.4, 124.4, 64.1, 43.6, 39.5, 13.4 and 12.0.

Diethylammonium 8-[(diethylamino)carbonyl]-1-naphthoate **31**. —A mixture of naphthalic anhydride (2.691 g, 13.60 mmol) and diethylamine (50 ml) was heated to reflux for 36 hours and cooled. The diethylamine was removed under reduced pressure to give the *diethylammonium 8-[(diethylamino)carbonyl]-1-naphthoate* **31** (4.672 g, *ca.* 100%) as a white solid which required no further purification, υ_{max} (film)/cm^{-1} 3300, 3289, 3273, 3258, 3222, 3206, 3192, 3072, 1769, 1735; δ_H(300MHz, $CDCl_3$) 7.9-7.7 (3H, m, ArH), 7.5-7.4 (3H, m, ArH), 3.72 (1H, m, $NCH_AH_BCH_3$), 3.42 (2H, m, CH_2), 3.26 (1H, m, $NCH_AH_BCH_3$), 2.79 (4H, q, *J* 7.3, 2 × CH_2), 1.34 (3H, t, *J* 7.1, CH_3), 1.14 (6H, t, *J* 7.3, 2 × CH_3) and 1.08 (3H, t, *J* 7.1, CH_3); δ_C(75 MHz, $CDCl_3$) 174.3, 172.0, 135.4, 134.3, 131.0, 129.7, 128.9, 127.1, 126.5, 126.0, 125.3, 124.4, 44.3, 41.3, 39.4, 13.7, 13.0 and 10.9; *m/z* (FAB) 270 (22%, M^+), 289 (100%), 176 (100%), 177 (100%) and 179 (100%).

8-[(Diisopropylamino)carbonyl]-1-naphthoic acid **32**. —*n*-Butyllithium (3.83 ml of a 1.6 M solution in hexanes, 6.13 mmol) was added to a solution of diisopropylamine (1.03 ml, 7.35 mmol) in THF (2 ml) at 0 °C under an atmosphere of nitrogen. After 20 minutes, a solution of naphthalic anhydride (578 mg, 2.92 mmol) in THF (10 ml) at 0 °C was added. The dark brown solution was stirred for a further 3 hours. Glacial acetic acid (2 ml) was added, and the mixture was extracted with dichloromethane (4 × 15 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude product, which was purified by flash chromatography on silica gel (45:1 dichloromethane-methanol + 1% glacial acetic acid) to give the *acid* **32** (1.794 g, 57%) as a sticky pale yellow solid. υ_{max} (film)/cm^{-1} 3110, 3054, 2976, 2934, 2878, 2618, 1725, 1696, 1624, 1583; δ_H(300 MHz, $CDCl_3$) 8.64 (1H, bs, OH), 7.95 (1H, dd, 8.2 and 1.1, ArH), 7.91 (1H, dd, *J* 7.7 and 1.9, ArH), 7.72 (1H, dd, *J* 7.1 and 1.4, ArH), 7.48 (3H, m, ArH), 4.28 (1H, septet, *J* 6.6, NCH), 3.60 (1H, septet, *J* 6.9, NCH), 1.63 (3H, d, *J* 6.9, CH_3), 1.54 (3H, d, *J* 6.9, CH_3) and 1.33 (6H, d, *J* 6.6, 2 × CH_3);

δ_C(75 MHz, $CDCl_3$) 176.6, 172.2, 171.5, 134.7, 134.1, 133.8, 131.8, 131.1, 130.3, 128.5, 126.9, 126.0, 124.8 and 51.7, 46.3, 20.8, 20.7, 20.2 and 20.2; *m/z* (CI) 300 (100%, M+H$^+$) and 256 (65%, M–*i*-Pr); *m/z* (EI) 299 (5%, M$^+$) and 91 (100%). (Found: M+H$^+$, 300.1610. $C_{18}H_{21}NO_3$ requires *M*+H, 300.1600).

Methyl 8-[(diisopropylamino)carbonyl]-1-naphthoate **33**. —A solution of potassium hydroxide (0.929 g, 16.56 mmol) in 96% ethanol (23 ml) was added to a stirred solution of *N*-methyl-*N*-nitroso-*p*-toluenesulphonamide (4.971 g, 23.20 mmol) in diethylether (60 ml) at 0 °C. After 5 minutes, the ethereal diazomethane solution was distilled. The etheral diazomethane was added in small portions to a solution of the acid **32** (756 mg, 2.53 mmol) in absolute ethanol (10 ml) until gas evolution had ceased and the solution became pale yellow. The solvent was removed under reduced pressure to give a crude product which was purified by flash chromatography on silica gel (4:1 petroleum ether–EtOAc) to afford the *ester* **33** (527 mg, 67%) as a sticky pale yellow solid, λ_{max}/nm (ε_{max}) (CH_2Cl_2) 232 (31280) and 294 (7378), R_f 0.39 (2:1 petroleum ether–EtOAc). υ_{max} (film)/cm^{-1} 1725, 1626, 3054, 2975, 2959, 2934, 2877; δ_H(300 MHz, $CDCl_3$) 8.0-7.4 (6H, m, ArH), 4.29 (1H, septet, *J* 6.6, NCH), 3.99 (3H, s, OCH_3), 3.59 (1H, septet, *J* 6.9, NCH), 1.71 (3H, d, *J* 6.7, NCHC*H*$_3$), 1.54 (3H, d, *J* 6.7, NCHC*H*$_3$), 1.42 (3H, d, *J* 6.7, NCHC*H*$_3$) and 1.32 (3H, d, *J* 6.6, NCHC*H*$_3$); δ_C(75 MHz, $CDCl_3$) 171.2, 169.1, 135.4, 131.9, 130.1, 130.1, 129.9, 128.4, 127.4, 126.0, 124.8, 124.7, 52.5, 51.5, 45.7, 21.0, 20.6, 20.4 and 20.2; *m/z* (CI) 314 (100%, M+H$^+$) and 213 (18%, M-N^{i}Pr$_2$); *m/z* (EI) 313 (6%, M$^+$), 213 (91%, M–N*i*-Pr$_2$) and 135 (100%). (Found: M$^+$, 313.1683. $C_{19}H_{23}NO_2$ requires *M*, 313.1678).

Alternatively, oxalyl chloride (0.16 ml, 1.86 mmol) was added dropwise to stirred a solution of acid **32** (172 mg, 0.58 mmol) in dichloromethane at 0 °C. After 30 minutes anhydrous methanol (1 ml, excess) was added, and the mixture was warmed to room temperature over 30 minutes. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel (4:1 petroleum ether–EtOAc) to afforded *ester* **33** (38 mg, 21%) as a pale yellow solid.

N, N-Diisopropyl-8-hydroxy-1-naphthamide **35** —*n*-Butyllithium (31 ml of a 1.6 M solution in hexane) was added dropwise to a stirred solution of diisopropylamine (6.9 ml, 49 mmol) in dry THF (70 ml) under nitrogen at –78 °C. After 20 min at –78 °C, a solution of lactone **34**[49] (6.8 g, 41 mmol) in THF (50 ml) was added dropwise. The solution turned deep red. After 4 h at -78°C, saturated NH_4Cl was then added and the mixture was warmed to room temperature and extracted with dichloromethane (2 × 60 ml). The extracts were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. Flash chromatography (2:1 petroleum ether–EtOAc) gave the *amide* **35** (9.7g, 87%) as colourless plates, m.p. 177-180 °C; R_f 0.20 (3:1 petroleum ether–EtOAc); υ_{max} (film)/cm^{-1} 3049 and 1605; δ_H(300 MHz, CDCl3) 8.5 (1H, s, OH), 7.75 (1H, d, *J* 7, ArH^2), 7.40 (1H, t, *J* 7, ArH), 7.24 (1H, d, *J* 7, ArH), 7.22(1H, d, *J* 8, ArH), 7.00 (1H, t, *J* 8, ArH), 6.64 (1H, d, *J* 7.5, ArH^7), 3.75 (1H, septet, *J* 7, CHN), 3.6 (1H, septet, *J* 7, CHN), 1.68 (3H, d, *J* 7, CHC*H*$_3$), 1.65 (3H, d, *J* 7, CHC*H*$_3$), 1.12 (3H, d, *J* 7, CHC*H*$_3$ and 1.08 (3H, d, *J* 7, CHC*H*$_3$); δ_C(75 MHz, $CDCl_3$) 174.2 (C=O), 135.1, 133.3, 128.4, 126.8, 126.4,

124.5, 122.3, 121.4, 119.2, 111.9, (Ar), 51.5, 45.9 (2 ×CH), 20.7, 20.1, 19.6 and 19.5 (4 ×CH_3). (Found: M^+, 271.1579; C, 74.95; H, 7.65; N, 5.12%. $C_{17}H_{21}NO_2$ requires *M*, 271.1572; C, 75.3; H 7.7; N 5.2%).

N,N-Diisopropyl-8-methoxy-1-naphthamide **36**. —Potassium carbonate (70g, 0.5 mol) and iodomethane (63 ml, 1 mol) was added to a stirred solution of the naphthamide **35** (27.3g, 0.1 mol) in acetone (700 ml) and the mixture was heated to reflux for 24 h. The mixture was cooled and filtered and the filtrate was evaporated. The residue was recrystalised from petroleum ether to give the methyl ether **36** (35.4 g, 95%) as white prisms, m.p. 182-186 °C; R_f 0.32 (1:1 petroleum ether–EtOAc); υ_{max} (film)/cm^{-1} 2959 and 1628; δ_H(300 MHz, $CDCl_3$), 7.80 (1H, d, *J* 8, ArH^2), 7.50 (3H, m, ArH), 7.30 (1H, t, *J* 7, ArH), 6.80 (1H, d, *J* 7, ArH), 4.00 (3H, s, OMe), 3.60 (2H, m, NCH ×2), 1.70 (3H, d, *J* 7, NCHC*H*$_3$), 1.68 (3H, d, *J* 7, NCHC*H*$_3$), 1.08 (3H, d, *J* 7, NCHC*H*$_3$) and 1.05 (3H, d, *J* 7, NCHC*H*$_3$); δ_C(75 MHz, $CDCl_3$) 171.5 (N–C=O), 155.4, 135.1, 134.6, 127.7, 126.2, 125.8, 123.3, 121.4, 120.8, 105.3 (Ar), 55.1 (OCH_3), 50.7, 45.3 (2 ×CHN), 29.6, 20.8, 20.3 and 19.5 (4 ×CH_3). (Found: M^+, 285.1721. $C_{18}H_{23}NO_2$ requires *M*, 285.1729).

N,N-Diisopropyl-8-(dimethylamino)-2-formyl-1-naphthamide **37**. —Naphthamide **15** (0.5 g, 1.7 mmol) in THF (20 ml) was added to a stirred solution of *sec*-butyllithium (7.4 ml of a 1.3 M solution in hexane) under nitrogen at –78°C. After 1 h at –78°C, DMF (1 ml, excess) in THF (10 ml) was added dropwise and the mixture was allowed to warm to room temperature over 1 h, poured into water and extracted with ether. The combined organic fractions were concentrated under reduced pressure to give a crude product which was recrystallised from ethyl acetate to yield the *aldehyde* **37** (0.47g, 86%) as yellow prisms, m.p. 147-150 °C; R_f 0.27 (7:1 petroleum ether–EtOAc); υ_{max} (film)/cm^{-1} 2967, 1682 and 1627 (N–C=O); δ_H(300 MHz, $CDCl_3$), 10.3 (1H, s, CHO), 7.95 (1H, d, *J* 8.5, ArH^3), 7.78 (1H, d, *J* 8.5, ArH^4), 7.54 (1H, d, *J* 7, ArH^6), 7.50 (1H, t, *J* 8, ArH^7), 7.26 (1H, d, *J* 7, ArH^5), 3.45 (1H, septet, *J* 7, NCH), 2.86 (1H, septet, *J* 7, NCH), 2.80 (3H, s, NCH_3), 2.50 (3H, s, NCH_3, 1.60 (3H, d, *J* 7, $NCHCH_3$), 1.56 (3H, d, *J* 7, $NCHCH_3$), 0.85 (3H, d, *J* 7, $NCHCH_3$) and 0.75 (3H, d, *J* 7, $NCHCH_3$); δ_C(75 MHz, $CDCl_3$) 192.1 (C=O), 167.1 (N-C=O), 153.7, 140.5, 138.0, 130.4, 129.2, 129.0, 126.0, 124.7, 122.5, 118.1 (Ar), 50.9, 50.2 ($(NCH_3)_2$), 46.3, 43.9 ($N(CH)_2$), 20.7, 20.5, 20.4 and 19.4 (4 ×CH_3). (Found: M^+, 326.2004. $C_{20}H_{26}N_2O_2$ requires *M*, 326.1994).

N,N-Diisopropyl-8-[(dimethylamino)methyl]-2-formyl-1-naphthamide **38**. —Naphthamide **17** (3 g, 9.6 mmol) in THF (40 ml) was added to a stirred solution of *sec*-butyllithium (7.4 ml of a 1.3 M solution in hexane) under nitrogen at –78°C. After 1 h at –78°C, DMF (4 ml, excess) in THF (50 ml) was added dropwise and the mixture was allowed to warm to room temperature over 1 h, poured into water and extracted with ether. The extracts were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was recrystallised from ethyl acetate to give the *aldehyde* **38** (1.9g, 60%) as white prisms, m.p. 151-154 °C; R_f 0.13 (EtOAc); υ_{max} (film)/cm^{-1} 2965, 1686 and 1628; δ_H(300 MHz; $CDCl_3$) 10.2 (1H, s, CHO), 8.10 (1H, d, *J* 7.5, ArH^3), 8.05 (1H,

d, *J* 7.5, ArH[4]), 7.95 (1H, d, *J* 7.5, ArH[7]) 7.84 (1H, d, *J* 7.5, ArH[5]), 7.68 (1H, t, *J* 7.5, ArH[6]), 4.35 (1H, d, *J* 16, $(CH_3)_2NCH_AH_B$), 4.00 (1H, d, *J* 16, $(CH_3)_2NCH_AH_B$), 3.70 (1H, septet, *J* 6.5, NCH), 3.25 (1H, septet, *J* 6.5, NCH), 2.45 (6H, s, NMe_2), 1.82 (3H, d, *J* 7, $NCHCH_3$), 1.73 (3H, d, *J* 7, $NCHCH_3$), 1.10 (3H, d, *J* 7, $NCHCH_3$) and 0.96 (3H, d, *J* 7, $NCHCH_3$), δ_C(75 MHz, $CDCl_3$) 191.5 (C=O), 169.0 (N–C=O), 140.2, 137.5, 137.4, 130.7, 130.4, 128.8, 128.2, 127.9, 127.2, 121.5 (Ar), 60.1, 51.3 (CH_2NMe_2), 45.9, 45.7 (CH ×2), 20.2, 19.7 and 19.6 (CH_3 ×4). (Found: M^+, 340.2145. $C_{21}H_{28}N_2O_2$ requires *M*, 340.2151).

N,N-Diisopropyl-2-formyl-8-methoxy-1-naphthamide **39**. —In the same way, naphthamide **36** (5 g, 17.5 mmol) gave a crude product which was recrystallised from ethyl acetate to yield the *aldehyde* **39** (4.6 g, 85%) as white prisms, m.p. 190-192 °C; R_f 0.32 (4:1 petroleum ether–EtOAc); υ_{max} (film)/cm^{-1} 2959, 1688 and 1629; δ_H(300MHz; $CDCl_3$) 10.2 (1H, s, CHO), 8.04 (1H, d, *J* 8.5, ArH[3]), 7.85 (1H, d, *J* 8.5, ArH[4]), 7.58 (1H, t, *J* 8, ArH[6]), 7.50 (1H, d, *J* 8, ArH[7]), 6.98(1H, d, *J* 8, ArH[5]), 4.00 (3H, s, OMe), 3.64 (1H, septet, *J* 7, CHN), 3.46 (1H, septet, *J* 7, CHN), 1.74 (3H, d, *J* 7, $NCHCH_3$), 1.70 (3H, d, *J* 7, $NCHCH_3$), 1.04 (3H, d, *J* 7, $NCHCH_3$) and 1.00 (3H, d, *J* 7, $NCHCH_3$); δ_C(75 MHz, $CDCl_3$) 191.1 (CHO), 167.8 (N–C=O), 156.8, 140.0, 137.9, 129.7, 129.5, 128.5, 127.7, 126.2, 125.8, 123.2, 122.7 (Ar), 55.1, 50.6, 20.3, 20.2, 19.5 and 19.3. (Found: M^+, 313.1679. $C_{19}H_{23}NO_3$ requires *M*, 313.1678).

X-ray crystallography

Crystal data for **12a** (E = Me): $C_{22}H_{33}N_1O_1$, M_r = 327.49. A colourless prism crystal, (ca. 0.20 x 0.30 x 0.50 mm^3) was mounted on a glass fibre and analysed with a Bruker SMART 1K CCD diffractometer equipped with an Oxford Cryosystems Cryostream cooler,[53] running at 123 K. Mo-Kα radiation, (λ = 0.71073 Å), Orthorhombic, space group $P2_12_12_1$, *a* = 10.348(3), *b* = 11.7521(14), *c* = 15.909(3) Å, *V* = 1934.8(8) $Å^3$, *Z* = 4, ρ_{calcd} = 1.124 Mg m^{-3}, μ(Mo-Kα) = 0.067mm^{-1}. *F*(000) = 720. The data collection nominally covered a sphere of reciprocal space by a combination of five sets of exposures; each exposure set had a different φ angle for the crystal and each exposure covered 0.3° in ω in 30 seconds. The crystal-to-detector distance was 4.909 cm. Coverage of the unique set was 100% complete to θ = 26.36°, (Data truncated at 0.80Å). Data reduction was performed with the program SAINT V5.10.[54] Crystal decay was monitored by repetition of the first 50 frames of data at the end of data collection and analyzing the duplicate reflections. Area detector scaling and absorption corrections were performed by SADABS.[54] This correction was used to scale the frames of data and to correct for absorption of the primary beam by the crystal support using the method of Blessing.[55] A correction for absorption of the primary beam by the crystal was not applied. Total number of reflections collected = 19260 (θ_{min} = 2.15°, θ_{max} = 26.36°), index limits *h* –12 to 12, *k* –14 to 14 and *l* –19 to 19; independent reflections = 3953; R_{int} = 0.0176, 3849 reflections were observed, ($I > 2.0\sigma(I)$). Hydrogen atoms were place geometrically and refined with a riding model (including free rotation about the C-C bond for methyl groups), and with U_{iso} constrained to 1.2 (1.5 for methyl groups) x U_{eq} of the carrier atom. Refinement on F^2 with 223 parameters

gave R_1 = 0.0279, wR^2 = 0.0717 (all data), S = 1.007, Δ/σ_{max} = 0.000, Δ/σ_{mean} = 0.000. The absolute stereochemistry was not determined. Maximum and minimum residual electron density = 0.18 and –0.15 e $Å^{-3}$ respectively. All calculations were performed with SHELXTL Version 5.10 1998.[56] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-134156. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033, email: deposit@ccdc.cam.ac.uk).

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