Atropisomeric benzamides and naphthamides as chiral auxiliaries†

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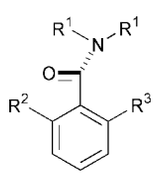
Atropisomeric compounds whose chirality resides in a rotationally restricted aryl–$CONR_2$ bond may be employed as chiral auxiliaries. The electron-withdrawing amide group causes problems in the diastereoselective functionalisation of enolates derived from atropisomeric phenyl esters, but a strategy based on atroposelective nucleophilic addition to a chiral aldehyde followed by stereospecific [3,3] sigmatropic rearrangement allows atropisomeric naphthamides to be used as auxiliaries. The auxiliaries are resolved by dynamic resolution during aminal formation using a proline-derived diamine.

Introduction

In a series of publications,[1–11] we have demonstrated that the stereogenic axis of hindered, atropisomeric tertiary aromatic amides of general structure **1** is capable of controlling high



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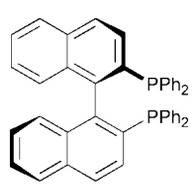


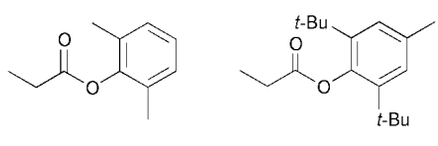
2

levels of stereoselectivity. We have also described two ways of making this class of atropisomeric compounds as single enantiomers,[12,13] both involving the control of axial stereochemistry by the conformational influence of an adjacent stereogenic centre. In this paper we describe our progress towards using atropisomeric amides as a new class of chiral auxiliaries. We begin with our attempts to design an auxiliary suitable for use in asymmetric *anti*-aldol chemistry, before moving on to the asymmetric synthesis of 2-substituted alcohols using a chiral, atropisomeric, *peri*-substituted naphthamide chiral auxiliary.[14] We found that the use of a hydrolysable ester linkage between the auxiliary and the substrate led to many problems, and for our successful development of the naphthamide auxiliary we use the strategy of linking the auxiliary to the substrate *via* a C–C bond, the auxiliary itself being an aldehyde. Our published[15] use of 2-dibenzylamino-3-phenylpropanal as a chiral auxiliary uses a similar strategy.

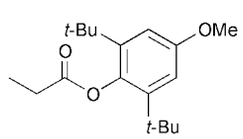
Atropisomeric chiral auxiliaries

Atropisomers which arise from restricted rotation in bonds to aromatic rings—and the vast majority of atropisomeric compounds fall into this category—can be seen as chiral modifications of the aromatic rings themselves. The famous and powerful atropisomeric phosphine ligands such as BINAP **2**[16] are in essence modifications to triphenylphosphine in which one of the phenyl rings is made chiral by incorporating it into the atropisomeric binaphthyl system. The philosophy of constructing chiral aryl groups by complexation to transition metals (principally chromium[17,18] for benzenoid rings and iron[19,20] for cyclopentadienyl) has also been fruitful in the invention of new chiral reagents, ligands and auxiliaries.

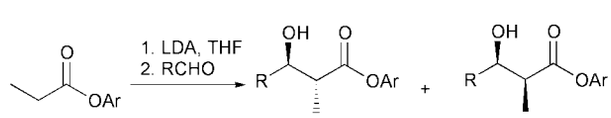
We were initially drawn to the idea of using atropisomeric chiral auxiliaries for aldol chemistry by the work of Heathcock,[21,22] who showed in 1980 that the propionate esters **3**–**5** of heavily substituted phenols undergo highly *anti*-selective aldol reactions with aldehydes (Scheme 1).



3 ("DMP ester") **4** ("BHT ester")



5 ("BHA ester")



3-5 *anti*-**6** *syn*-**6**

Scheme 1 *anti*-Aldol reactions with hindered phenyl esters.

The DMP ester **3** gives ratios of 88 : 12 to 86 : 14 *anti*-**6** : *syn*-**6** with aromatic aldehydes and α-unbranched aliphatic aldehydes, and pure *anti* products with α-branched aliphatic aldehydes (>98 : <2). The BHT and BHA esters **4** and **5** give only *anti*-aldols with all aldehydes. All are readily prepared from the commercially available phenols. The products **6** from the less selective DMP esters **3** may be hydrolysed; the BHT and BHA esters from **4** and **5** resist hydrolysis, but the latter may be cleaved oxidatively. The *anti*-selective aldol reactions of hindered aryl esters appear as key steps in synthetic routes to davanone,[23] lankanolide,[24] the pamamycins,[25] erythronolides A[26] and B[27] and the vitamin E side chain,[28] among others.[29,30]

† Further experimental details are available as supplementary data. For direct electronic access see http://www.rsc.org/suppdata/p1/b0/b004682p/

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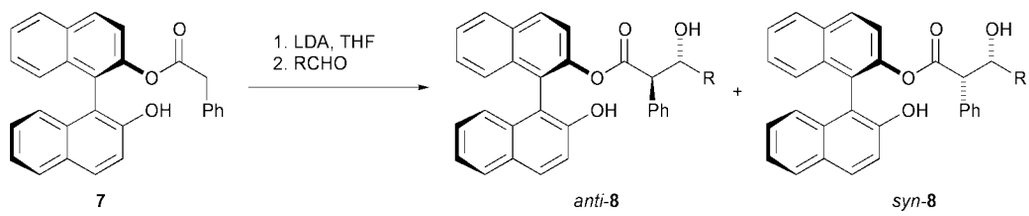
Table 1 Synthesis of the carbamoylphenols

R^1, R^2		R^3				
H, H	**11a**	*i*-Pr	**12a** 92%	**13a** 94%		**14a** 95%
NH_2, H	**11b** ⟶ MeI, Na_2CO_3,					
NMe_2, H	**11c** ⟵ MeOH	*i*-Pr	**12c** 68%	**13c** 81%		**14c** 82%
–OCH_2O–	**11d**	*i*-Pr	**12d** 92%	**13d** 71%		**14d** 93%
OMe, H	**11e**	*i*-Pr	**12e** 85%	**13e** 91%	$Me_2S:BBr_3$, CH_2Cl_2	—
		Et	**12f** 90%	—		—
OH, H	**11g**	*i*-Pr	**12g** 88%	**13g** 60%		**14g** 32% ⟵ NaI, HCl,
OCOEt, H	—	*i*-Pr	—	—		**14h** 53% acetone
OMOM, H	—	*i*-Pr	**12i** 93% ⟵ NaH, MOMCl, THF, 0 °C	**13i** 45%		**14i** 93% ⟵ 50 °C, 41%



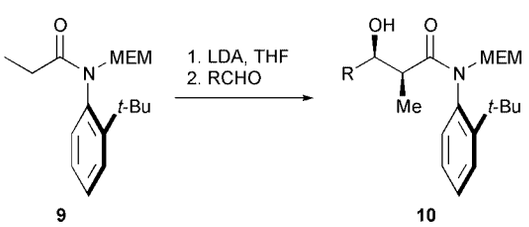
7 *anti*-**8** *syn*-**8**

Scheme 2 Fuji's *anti*-aldol with an atropisomeric, hindered ester.

A chiral version of these hindered aryl groups offers the chance to achieve *anti*-diastereoselectivity in an enantioselective fashion. Previous studies in this area include those of Fuji and co-workers,[31] who have reported that the enolate of the binaphthyl ester **7** reacts with aldehyde electrophiles to give the *anti*-aldol products *anti*-**8** with high diastereoselectivity and in good yields (Scheme 2).

Our aim in the work described in this paper was to achieve similar *anti*-selectivity in aldol reactions of esters derived from hindered atropisomeric phenols bearing tertiary amide substituents. We hoped to exploit the Lewis-basicity of the amide group to enhance the degree of chelation control in the aldol transition state. We hoped then to develop an asymmetric *anti*-aldol reaction by using enantiomerically pure atropisomeric amides.

Enantiomerically pure *non-biaryl* atropisomers have only recently found uses in asymmetric synthesis, and the most well-studied class to date are anilides related to **9** (Scheme 3). These



9 **10**

Scheme 3 *syn*-Aldol reaction of an atropisomeric anilide.

have been obtained in enantiomerically enriched form[32–35] and employed as chiral auxiliaries to asymmetric enolate alkylations and aldol reactions,[32,33] cycloadditions[34] and iodolactonisations.[35] Simpkins and co-workers achieved high *syn*-diastereoselectivity in aldol reactions of atropisomeric anilide **9** derived from *ortho-tert*-butylaniline (Scheme 3).[36,33]

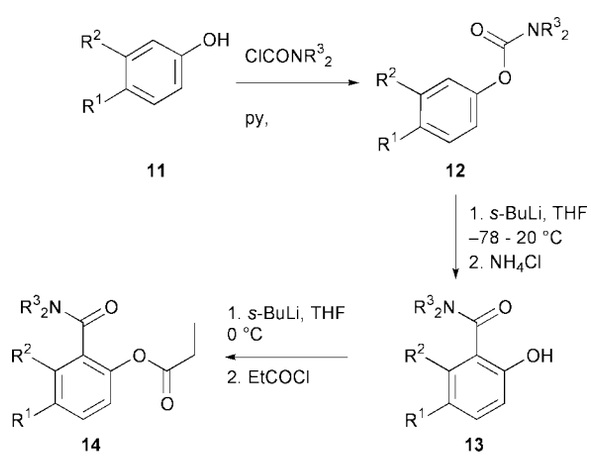
We[12] and others[37] have recently reported enantioselective routes to atropisomeric benzamides **2** and the related naphthamides, but uses for enantiomerically enriched atropisomeric benzamides have been confined to NADH model studies[38] and components of tachykinin NK_1 receptor agonists.[39]

Results

Aldol reactions of *N*,*N*-dialkylcarbamoylphenyl esters

Our first task was to establish whether aldol reactions of the esters of amide-substituted phenols were even possible, irrespective of stereochemistry.

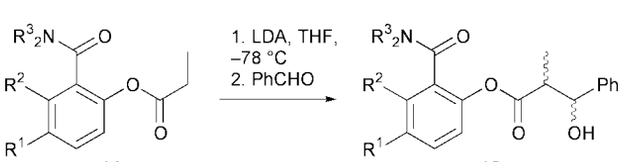
Our first reactions were attempted using 2-hydroxybenzamide **13a**. Phenol **11a** and diisopropylcarbamoyl chloride in refluxing pyridine gave the carbamate **12a**, which was converted to the amide **13a** using the "anionic ortho-Fries" rearrangement developed by Snieckus[40]—essentially an intramolecular acyl transfer reaction of an ortholithiated carbamate. The ortholithiated carbamate is stable at −78 °C, but undergoes rearrangement to the phenoxide on warming and thence gives **13a** on aqueous quench (Scheme 4). Esterification with propionyl chloride gave propionate **14a** (Table 1).



11 **12** **14** **13**

Scheme 4 Synthesis of propionate esters of 2-(*N*,*N*-dialkyl)carbamoylphenols.

An attempted aldol reaction between **14a** and benzaldehyde under standard conditions (Scheme 5) failed. Treatment of **14a**



14 **15**

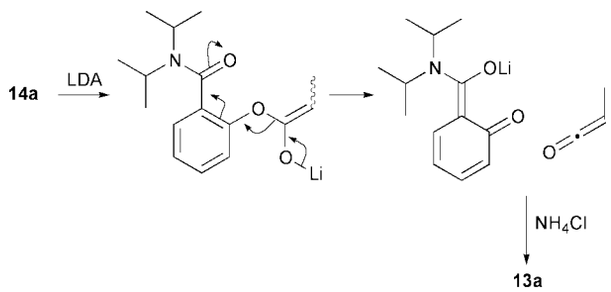
Scheme 5 Attempted aldol reactions of propionates **14**.

with LDA at −78 °C and quenching with benzaldehyde gave only 2-hydroxybenzamide **13a** and recovered starting material **14a**: no aldol products **15** were observed (Table 2, entry 1). The formation of **13a** can be explained by decomposition of the enolate according to Scheme 6. Compound **13a** was also

Table 2 Attempted aldol reactions of carbamoylaryl esters

Entry	Starting material	Conditions	Electrophile	Aldol product	Remaining starting material	Decomposition product
1	**14a**	LDA, −78 °C	PhCHO	0	**14a**, n/d	**13a**, n/d
2	**14a**	LDA, −78 °C	NH_4Cl	—	**14a**, 67[a]	**13a**, 33[a]
3	**14c**	LDA, −78 °C	NH_4Cl	—	**14c**, 58[a]	**13c**, 42[a]
4	**14d**	LDA, −78 °C	NH_4Cl	—	**14d**, 68[a]	**13d**, 32[a]
5	**17**	LDA, −78 °C	NH_4Cl	—	**17**, 75[a]	**16**, 25[a]
6	**14g**	2 × LDA, −78 °C	NH_4Cl	—	**14e**, 100[a]	—
7	**14g**	2 × LDA, −78 °C	PhCHO	62% **18** (31 : 39 *anti* : *syn*)[b]	n/d	n/d
8	**25c**	LDA, −78 °C	NH_4Cl	—	**25c**, 40[a]	**22c**, 60[a]
9	**25f**	2 × LDA, −78 °C	PhCHO	41% *anti*-**26** 32% *syn*-**26**	**25f**, 10	**22f**, 13

[a] Estimated by NMR. [b] From ratio of reduction products **20**.



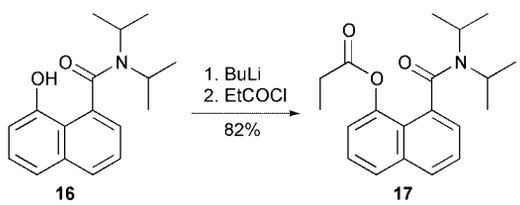
Scheme 6 Decomposition of the enolate of **14a**.

formed when the enolate was quenched at −78 °C with ammonium chloride (entry 2).

We assume the problem arises from the stability of the phenoxide, stabilised as it is by conjugation with the amide carbonyl group. We therefore next made the amino-substituted hydroxybenzamide **13c**, hoping that destabilisation of the phenoxide by the *para*-amino substituent would disfavour the competing elimination. Compound **13c** was made from 4-aminophenol **11b** by methylation to give **11c**, carbamate formation to give **12c** and anionic ortho-Fries rearrangement to **13c**. Unfortunately, formation of the lithium enolate of the propionate ester **14c** of the amino-substituted phenol **13c** still led to decomposition by elimination of **13c** (entry 3).

A successful atropisomeric chiral auxiliary would necessarily be a 2,6-disubstituted benzamide, or it would lack conformational stability.[41] We wondered whether the enforced perpendicular conformation[4] of a 2,6-disubstituted amide would furthermore lessen the ability of the amide group to stabilise the phenoxide anion by conjugation. Both 2-substituted and 2,6-disubstituted benzamides adopt a perpendicular conformation in the ground state,[4] but we expected rotation of the latter into a conformation allowing some degree of conjugation to incur a significantly greater cost in steric strain. Our next target phenol was therefore **13d**, in which the methylenedioxy group has a dual role: it increases the electron density on the ring, and blocks any overlap of the amide π* with the conjugated phenoxide orbitals. The synthesis of **13d** was again straightforward: the only additional point of interest is the regioselectivity of the anionic ortho-Fries rearrangement of **12d**, which followed precedent:[40] lithiation occurred in between the two *ortho*-directors (carbamate and alkoxy) to give the 1,2,3,4-tetrasubstituted phenol **13d**. Esterification gave **14d**, but unfortunately the lithium enolate of **14d** was again unstable, and collapsed to give significant amounts of **13d** at −78 °C (Table 2, entry 4).

We briefly investigated the possibility of "insulating" the phenoxide from the electronic effect of the amide by attaching the two groups to the separate rings of a naphthalene system. To maintain the stereochemical communication between the two groups necessary for any successful asymmetric induction, we decided to attempt an aldol reaction on the enolate of esters of the 8-hydroxynaphthamide **16**. This type of compound was



particularly attractive because it can be made from naphthalic anhydride by a high-yielding route,[42] and the *peri*-relationship between the hydroxy group and the amide is expected to result in good conformational stability. Esterification of **16** and enolisation of **17** with LDA however still led to decomposition by elimination (Table 2, entry 5).

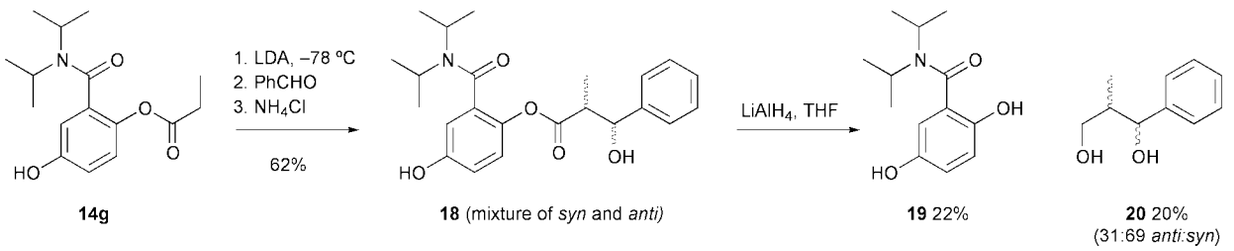
We finally concluded that to have any chance of preventing the decomposition of the enolate, we would need to make it a dianion. We therefore decided to try next the dihydroxybenzamide **13g**. We expected problems with a dianionic ortho-Fries rearrangement of **12g** (which we required later in the project), so we made **13g** by demethylation of **13e** using boron tribromide–dimethyl sulfide complex. Compound **13e** was easily made by the usual route from 4-methoxyphenol **11e** (Table 1). Esterification of the unsymmetrical diol **13g** gave a separable mixture of the desired monoester **14g** and the diester **14h**. Encouragingly, treatment of the monoester **14g** with two equivalents of LDA at −78 °C and quenching with saturated aqueous ammonium chloride gave starting material only (no decomposition products) by ^{1}H NMR (Table 2, entry 6).

Lack of regioselectivity in the esterification of **13g** hampered further work with **14g**, so we decided to turn to a protecting group for the *para*-hydroxy group which we could retain until after esterification with propionyl chloride. Table 1 shows how hydroquinone **11g**, with one equivalent of diisopropylcarbamoyl chloride in pyridine, gave carbamate **12g** in good yield. The remaining hydroxy group of **12g** was protected with chloromethyl methyl ether to give carbamate **12i** in excellent yield. Anionic Fries rearrangement of **12i** gave **13i**, which was esterified to give **14i** and then selectively relieved of its MOM group by sodium iodide in acetone in the presence of catalytic conc. HCl, giving cleanly **14g**.

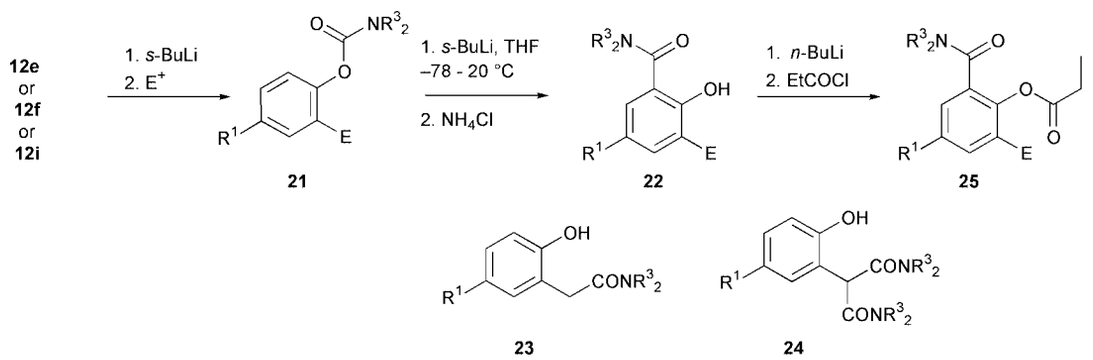
The result of the aldol reaction of **14g** is shown in Scheme 7 and Table 2, entry 7. Treatment of a solution of two equivalents of LDA in THF at −78 °C with ester **14g** and then benzaldehyde afforded a mixture of aldol products **18** in 62% yield after purification. Evaluation of the diastereoisomeric ratio by NMR was complicated by slow rotation about the amide Ar–CO and C–N bonds. However, lithium aluminium hydride in refluxing THF gave a readily identifiable mixture of the diols **20** in a diastereoisomeric ratio of 31 (*anti*) : 69 (*syn*) (identification of

Table 3 Ortholithiation, anionic ortho-Fries rearrangement and esterification

R^1	R^3	E					
OMe	*i*-Pr	Me	**21a**, 96%	**22a**, 18%	**23a**, 26%	—	—
OMe	Et	Me	**21b**, 95%	**22b**, 20%	**23b**, 13%	**24b**, 8%	—
OMe	*i*-Pr	CD_3	**21c**, 86%	**22c**, 86%	—	—	**25c**, 72%
OMe	*i*-Pr	$SiMe_3$	**21d**, 70%	**22d**, 97%	—	—	**25d**, 99%
OMOM	*i*-Pr	$SiMe_3$	**21e**, 47%	**22e**, 82%	—	— NaI, HCl	**25e**, 89%
OH	*i*-Pr	$SiMe_3$	—	**22f**	—	— acetone	**25f**, 80%
						— 50 °C	



Scheme 7 Aldol reaction of **14g**.



Scheme 8 2,6-Disubstituted phenyl esters by regioselective anionic ortho-Fries rearrangement.

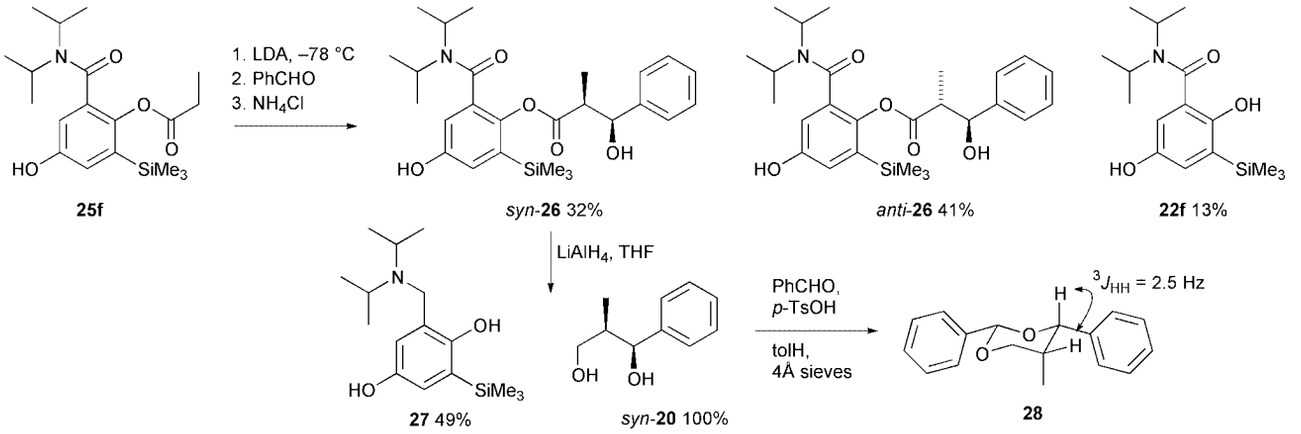
the diastereoisomers described below). These conditions also reduced the amide to **19** in 22% yield.

Encouragingly, we had now confirmed that the dianion enolates were stable, and underwent clean aldol reactions. We were, at this stage, hopeful that the 2:1 *syn*-selectivity would be overturned by introduction of a second substituent *ortho* to the ester linkage (in the manner of **5**) so we decided to use ortholithiation of the carbamate precursor to achieve this. We took carbamates **12e** and **12f**, lithiated them with *s*-BuLi at −78 °C, and added methyl iodide to give **21a** and **21b** in 95 and 96% yields respectively (Scheme 8). The anionic Fries rearrangement of these compounds to **22a** and **22b** was surprisingly complicated by a lack of regioselectivity in their lithiation reactions. Although lateral lithiation (*i.e.* lithiation at an *ortho* benzylic site) commonly dominates ortholithiation in amides,[43,9,44] even *ortho*-methyl substituted carbamates typically undergo clean anionic ortho-Fries rearrangement.[40] Not so **21a** and **21b**: both showed evidence of considerable lateral lithiation and migration of the amide substituent to the benzylic position (Table 3). Warming lithiated carbamate **21a** to ambient temperature and quenching with water afforded a mixture of the desired **22a** (18%), the product of lateral lithiation and rearrangement **23a** (26%) and remaining **21a** (24%). Judging the main difference between our molecules and those of Snieckus to be the nitrogen substituents, we next tried rearranging **21b**. The yield of the anionic ortho-Fries product **22b** (20%) was not increased by this change, and the by-products included not only the laterally rearranged **23b** (13%) and remaining **21b** (43%) but also its acylated analogue **24b** (8%), which presumably arises by intermolecular attack of lithiated **23b** on remaining unreacted **21b**. Snieckus obtained *ortho* migration in 70% yield for a similar *ortho*-methyl *N*,*N*-diethylcarbamate which differed only by lacking the *para*-methoxy substituent.[40] Presumably this is sufficient to disfavour metallation of the more electron-rich ring.

Snieckus has demonstrated the use of trimethylsilyl as a temporary blocking group for kinetically acidic sites, allowing control over the regioselectivity of deprotonation.[45] In our own work we have found that the magnitude of the kinetic isotope effect for low-temperature lithiation,[46] which has been shown experimentally to exceed 50 at −78 °C,[47] allows the use of deuterium substituents as protecting groups for carbon atoms, directing lithiation to other acidic sites in the molecule.[48] We decided to test both of these methods as a means of encouraging the anionic ortho-Fries rearrangement to become the major reaction pathway for compounds **21**. We ortholithiated carbamate **12e** and quenched with d_3-methyl iodide or chlorotrimethylsilane to give **21c** and **21d** in 86 and 70% yields respectively (Table 3).

Under the usual conditions (*sec*-butyllithium at −78 °C, followed by warming to 20 °C), both **21c** and **21d** underwent clean anionic ortho-Fries rearrangement to give **22c** and **22d** in excellent yield. The complete overturning of the regioselectivity of **21a**'s rearrangement is a remarkable testimony to the synthetic power of kinetic isotope effects.[48]

Esterification of **22c** and **22d** with *n*-butyllithium and propionyl chloride gave the esters **25c** and **25d** in good to excellent yield. Not surprisingly, a test exposure of the ester **25c** to LDA at −78 °C, quenching with saturated aqueous ammonium chloride, returned a mixture of phenol **22c** and recovered starting material **25c** in a ratio of 60:40 (Table 2, entry 8).



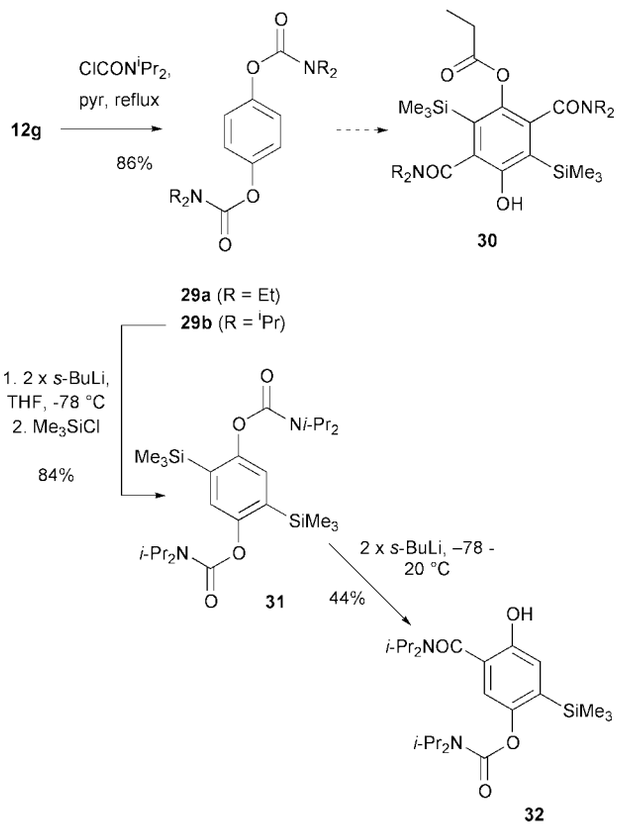
Scheme 9 Aldol reaction of **25f**.

In order to build on the encouraging results with enolate dianions (Table 2, entries 6 and 7), attempts were made to dealkylate the methyl ether **25c** with BCl_3 and TMSI which are reportedly more selective than BBr_3.[49,50] However BCl_3 (−78–0 °C) converted 31% of ester **25c** to the phenol **22c**. Addition of BCl_3 to ester **25c** at 0 °C and stirring for 8 minutes before quenching with water converted 60% to **22c**. After 48 h at ambient temperature, **25c** had not reacted with TMSI.

We decided to revert to the more readily removed protecting group, MOM, for protection of the second phenolic OH. Ortholithiation with *sec*-butyllithium, quenching with chlorotrimethylsilane, afforded *ortho*-substituted carbamate **21e** (Table 3) in a low yield of 47%. Anionic ortho-Fries rearrangement gave the phenol **22e** in a yield of 82%, which was esterified to give **25e** and deprotected (using sodium iodide in acetone with a catalytic amount of concentrated hydrochloric acid) to the phenolic ester **25f** in 80% yield.

Treatment of ester **25f** with two equivalents of LDA at −78 °C followed by benzaldehyde and work-up with saturated aqueous ammonium chloride (Scheme 9 and Table 2, entry 9) gave 73% combined yield (41% and 32%) of the two aldol products **26**, with only 13% of elimination product **22f**. Determination of the sense of diastereoselectivity at this stage was hampered by complex NMR data due to slow rotation in the amides **26**. The least polar diastereoisomer (32% yield) was reduced with lithium aluminium hydride in refluxing THF to afford the amine **27** and a single diol **20**. To determine the relative stereochemistry of **20**, it was converted to its benzylidene acetal **28**, whose $^3J_{HH}$ –C*H*MeC*H*(Ph)– coupling constant of 2.5 Hz indicated axial–equatorial, and hence *syn*, stereochemistry. The crude ratio of *anti*:*syn* aldol products from **25f** turned out to be 59:41.

We were pleased that the aldol reaction was now *anti*-selective, though disappointed that the selectivity was not higher, and that the phenol decomposition by-product was again appearing in the product mixture. To facilitate further studies, we decided to attempt to reduce the number of steps required to reach the model auxiliaries. Snieckus[51] had made compound **29a**, and it was hoped that the analogue **29b** (R = *i*-Pr) would lead to ester **30** in three further steps (Scheme 10). Ester **30** would have the oxy anion as well as the steric bulk required for good diastereoselectivity when reacted with an aldehyde. The dicarbamate **29b** was made in 86% yield from the phenol **12g** and subsequent double ortholithiation with two equivalents of *sec*-butyllithium, quenching with chlorotrimethylsilane, afforded **31** in 84% yield. Treatment of **31** with two equivalents of *sec*-butyllithium at −78 °C, warming to ambient temperature and stirring overnight afforded **32** in 44% yield with other minor unidentifiable products. Presumably the tetrasubstituted benzene **31** is too hindered to undergo deprotonation: the *sec*-butyllithium removes a trimethylsilyl group to give an anion which undergoes an anionic ortho-Fries rearrangement to give **32** after aqueous work-up.



Scheme 10 Attempted double anionic ortho-Fries rearrangement.

At this point we decided to abandon this route to a potential auxiliary. The problems posed by the phenyl ester linkage are too great for us to have a reasonable expectation of success in designing useful chiral auxiliaries. We decided to overcome this lack of stability in the auxiliary–substrate linkage by connecting the two through a C–C bond.[52] We had already demonstrated the use of a phenylalanine-derived aldehyde **38** as a C–C bonded auxiliary in the synthesis of 2-substituted primary alcohols,[15] and the strategy we used then is outlined in Scheme 11. The auxiliary **33**, an aldehyde, is chosen such that nucleophilic additions of vinyl anion equivalents are highly diastereoselective. This was true, as demonstrated by Reetz and co-workers,[53–55] for the phenylalanine-derived **38**, but central to our use of atropisomeric amides is our recent demonstration that 2-formylnaphthamides **39** also undergo extremely diastereoselective nucleophilic additions.[5,7] The addition of a vinyl anion equivalent (in general, we have used alkynyl nucleophiles followed by reduction) gives allylic alcohol **34**.

The enantiomerically and diastereoisomerically pure allylic alcohol **34** is functionalised to give **35** in such a way that stereospecific rearrangement (probably [3,3] sigmatropic) can be induced to give **36**. Finally, the auxiliary is recovered by oxidative cleavage of the alkene to give a pair of aldehydes, the recyclable auxiliary **33** and the 2-substituted aldehyde product **37**.

A similar approach has been used by Spino and Beaulieu,[56,57] who employed a terpene-derived ketone as an auxiliary in a similar route, by Thomas and co-workers, who have used lactic acid as the source of chirality (not truly an auxiliary as it was never recovered) in the synthesis of polyoxamic acid,[58] and by Larchevêque and co-workers in the synthesis of dipeptide isosteres.[59]

We decided to use **39** as the basis of our design for a new chiral auxiliary, aiming to introduce features which would lead to total stability about the Ar–CO bond (and therefore resistance to racemisation). We hoped to build on our understanding of the stereoselective additions of nucleophiles to **39**[5,7] and to exploit the shift of the double bond of **35** into conjugation with the aromatic ring in **36**. From previous work, we knew that the 8-substituents of aldehydes **40**, **41** and **42** led to much increased conformational stability, with the greatest effect being exerted by the 8-MeO group of **42**. A bonding interaction between the 8-substituent and the amide carbonyl, evident by X-ray crystallography, is responsible for this effect.[60] We therefore decided to start by studying the stereoselectivity of nucleophilic additions (Scheme 12) to **40**, **41** and **42**, which were all available by our published route.[42]

Table 4 summarises these results, and includes, for comparison, published results obtained with **39**.

Aldehyde **39** and its analogues had generally showed moderate *anti*-selectivity in additions of organolithiums such as BuLi and MeLi,[7] and we were pleased to find that BuLi added to **41** even more *anti*-selectively (entry 1). Unfortunately, the high level of *anti*-selectivity was not displayed by the unsaturated nucleophiles we need to use: both octynyllithium and ethynylmagnesium bromide gave only moderate *anti*-selectivity with **41** (entries 2 and 3). The *anti*-selective addition of octynyllithium contrasts with the moderately *syn*-selective addition of this nucleophile to **39**, and when we tried this reaction with **42** we again saw moderate *syn*-selectivity. The product of this reaction, *syn*-**46b**, was characterised by X-ray crystallography (Fig. 1), and allowed us continued confidence in our provisional assignment of *anti*-stereochemistry to the less polar diastereoisomer in all other cases.[4,6] The amino group of **41** must be playing a role in altering selectivity, perhaps by becoming involved in coordination with the aggregated organolithium nucleophile. With amino aldehyde **40**, octynyllithium showed no stereoselectivity at all.

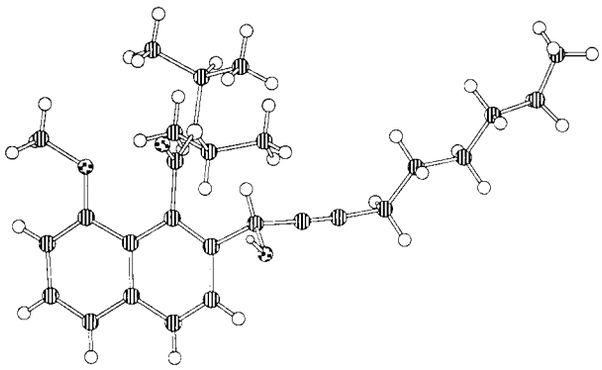
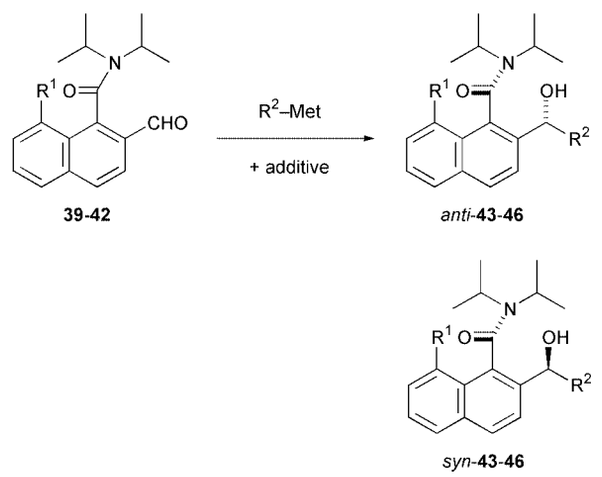
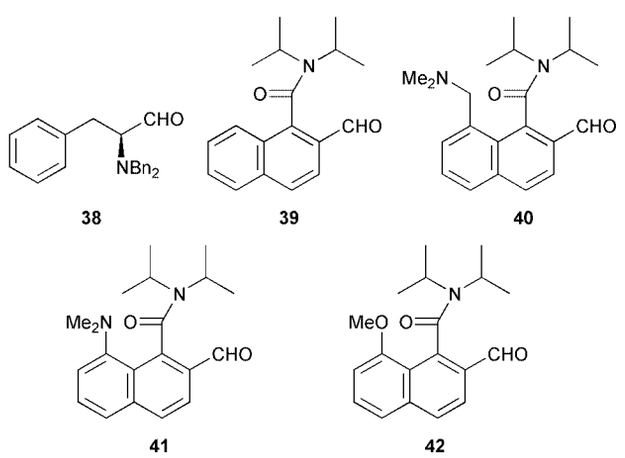


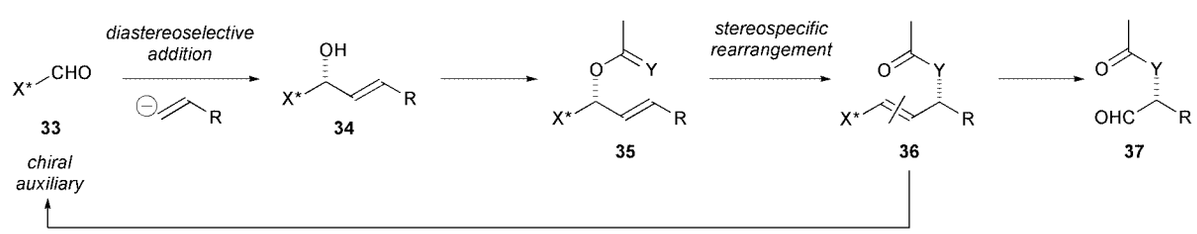
Fig. 1 X-Ray crystal structure of *syn*-**46b**.



Scheme 12 Nucleophilic additions to *peri*-substituted 2-formyl-1-naphthamides.

Alkyltriisopropoxytitaniums, bulky nucleophiles which react under non-chelation control,[61] had shown excellent *anti*-selectivity with **39**[7] (entries 4–6) but we found that with **40** this selectivity dropped substantially. With **41**, no alcohol products were observed—instead, the Lewis acidity of the titanium species in the reaction mixture had promoted lactonisation to **47**, **48**, or **49**, and even some reduction to **50** (presumably by hydride transfer from $BuTi(O\textit{i}\text{-}Pr)_3$). The other highly selective additions observed with **39** had been those of organolithiums in the presence of alkylaluminium reagents such as DIBAL-H or Me_3Al (entries 7–9).[7] Adding DIBAL-H to the reaction of octynyllithium with **40** increased the selectivity to 96:4, and extremely high levels of *anti*-selectivity resulted from the addition of octynyllithium to **41** in the presence of DIBAL-H. Not surprisingly, both reactions tended to be accompanied by reduction of the aldehyde: the addition to **41**





Scheme 11 Strategy for C–C bonded auxiliary control over new chiral centres.

Table 4 Stereoselective additions to 2-formyl-1-naphthamides (R = *n*-hexyl)

				39; R^1 = H		**40**; R^1 = Me_2NCH_2		**41**; R^1 = Me_2N		**42**; R^1 = MeO	
Entry	Nucleophile	R^2	Additive	Product, yield (%)[a]	Selectivity[b]	Product, yield (%)	Selectivity[b]	Product, yield (%)	Selectivity[b]	Product, yield (%)	Selectivity[b]
1	BuLi	Bu–	—	**43a**, 83	85:15	—	—	**45a**, 57	94:6	—	—
2	R–C≡C–Li	R–C≡C–	—	**43b**, 90	20:80	**44b**, 66[d]	50:50	**45b**, 88[d]	71:29	**46b**, 44[d]	25:75[e]
3	H–C≡C–MgBr	H–C≡C–	—	—	—	—	—	**45c**, 74[c]	75:25	—	—
4	R–C≡C–Ti(O*i*-Pr)$_3$	R–C≡C–	—	**43b**, 52	125:1	**44b**, 36[c]	67:33	**47**, 83	—	—	—
5	BuTi(O*i*-Pr)$_3$	Bu–	—	**43a**, 63	125:1	—	—	**48**, 15	—	—	—
								50, 49			
6	MeTi(O*i*-Pr)$_3$	Me–	—	**43d**, 99	300:1	—	—	**49**, 63	—	—	—
7	R–C≡C–Li	R–C≡C–	DIBAL-H	**43b**, 50	>99:1	—	—	**45b**, 53[c] or **51**, 88	96:4	**46b**, 65[c]	>99:1
8	R–C≡C–Li	R–C≡C–	Me_3Al	**43b**, 66	93:7	—	—	—	—	**46b**, 51[c]	97:3
9	BuLi	Bu–	Me_3Al	**43a**, 56	94:6	—	—	—	—	**46a**, 66[c]	95:5

[a] From ref. 7. [b] From ^{1}H NMR spectrum of crude mixture. [c] Isolated yield of major diastereoisomer. [d] Isolated yield of mixture of diastereoisomers. [e] Stereochemistry assigned by X-ray crystal structure of *syn*-**46b** (Fig. 1). Stereochemistry in other cases provisionally assigned by assuming that the *anti*-diastereomer is less polar.[4,6]

was quite capricious in this regard, and on one occasion generated 88% of the alcohol **51**.

At some small cost to selectivity, we found that the alternative, to use Me_3Al as the additive,[7] reliably gave moderate to good yield and good *anti*-selectivity. From the reaction of octynyllithium with **41** in the presence of 0.1 equiv. Me_3Al, for example, it was possible to isolate 51% yield of the *anti* alcohol *anti*-**46b**. Replacing trimethylaluminium with triethylaluminium led only to recovery of starting material.

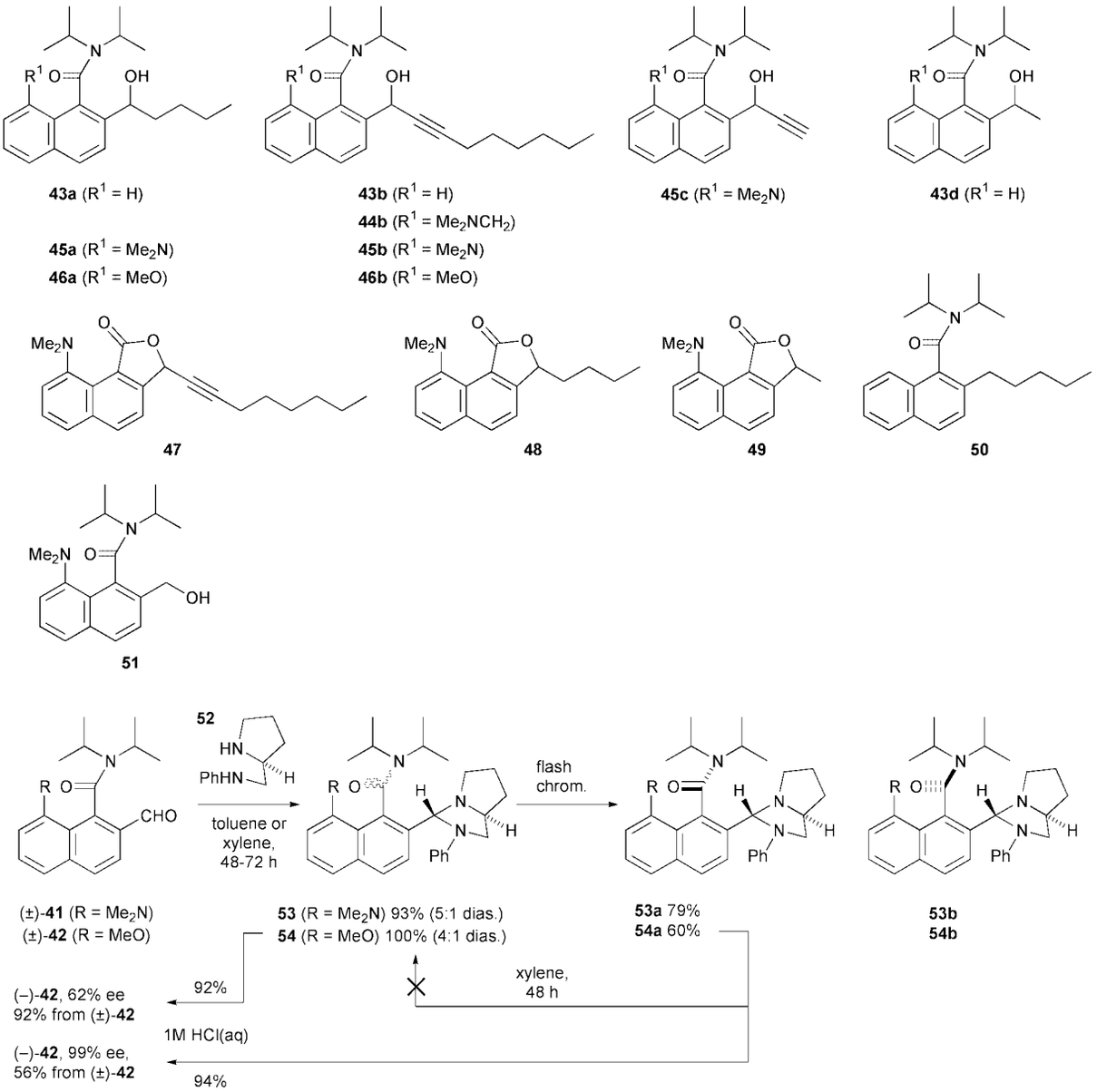
Although we experimented with selective additions to all three of **40**–**42**, the final decision to use **42** as the prospective chiral auxiliary was based on the stability of its derivatives to racemisation or epimerisation. We knew that **40** racemised considerably faster than **41** or **42**.[60] Compound **41** has a half-life for racemisation in dioxane solution of 6 days at 20 °C, even though it bears only a –CHO substituent *ortho* to the amide. (Trigonal substituents usually permit easy bond rotation.[41]) To assess the stability to epimerisation of its addition products, we took *anti*-**45a** and incubated it at 60 °C for 4 h. No sign of epimerisation to *syn*-**45a** was evident, suggesting a rate constant of $<1.4 \times 10^{-6}$ s^{-1} for this process, and hence a barrier to epimerisation of >120 kJ mol^{-1}. Compound **42** racemises almost 25 times more slowly than **41**, and this informed our final choice of **42** as auxiliary.

The next challenge was to resolve **41** and **42**. We decided to convert them to pairs of diastereoisomeric aminals[62] **53** and **54** by refluxing with the proline-derived diamine **52**.[63] We intended to use **52** as a resolving agent, aiming to separate the diastereoisomeric aminals by column chromatography. In the event, something more complex, and more useful, than a simple resolution took place (Scheme 13). Instead of forming in a 1:1 ratio, as would be expected for a simple resolution, the product aminals were formed with a significant excess (4 or 5:1) of one diastereoisomer over the other. We were unable to prove that the minor diastereoisomer is an atropisomer of the major, though this would account nicely for the enantiomeric excesses obtained when the aminals were hydrolysed back to the aldehydes (see below). Aminals derived from **52** typically form with high *exo*-selectivity for the new stereogenic centre.[64]

The stereogenic axis of the amide is inverting during the course of the aminal-forming reaction, though at this stage it was not clear to us whether this inversion was a racemisation of the starting material or an epimerisation of the product. The two diastereoisomers of each pair of aminals were separable by flash chromatography on alumina (though the minor diastereoisomers **53b** and **54b** turned out to be very unstable), and we were able to distinguish between these two possibilities by re-subjecting purified **54a** to the conditions of the reaction. No **54b** was formed, suggesting that the inversion is a racemisation of the starting material which occurs before aminal formation takes place. The temperatures of the reactions (110–140 °C) should racemise **41** and **42** in a matter of minutes.[60]

The 4:1 mixture of aminals **54** was hydrolysed to the aldehyde (−)-**42** in 92% yield. The aldehyde was formed in 62% ee by HPLC on a chiral stationary phase. Alternatively, the purified major aminal **54a** could be hydrolysed to give (−)-**42** with 99% ee.

Overall, the resolution has features of a dynamic resolution, because the starting material racemises as the resolution takes place. The dynamic resolution appears to be under kinetic control, since re-subjection of the purified product to the conditions of the reaction does not regenerate the same ratio of products as the reaction itself.[65] We had previously noted a dynamic *thermodynamic* resolution[66] during similar aminal formation from **39**,[12] but in that case (where R = H), the barrier to epimerisation of the product is significantly lower. Incidentally, that dynamic thermodynamic resolution was apparently accompanied by an inconsequential dynamic kinetic resolution in the opposite direction, which was overridden by the subsequent equilibration of the product diastereoisomers. For **53** and



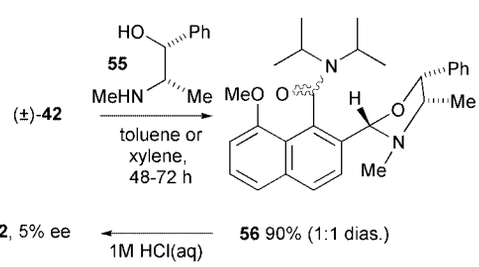
Scheme 13 Dynamic resolution of **41** and **42**.

54, our assignment of stereochemistry to **53a** and **54a** is not proven, but we chose to follow the precedent of the proven stereoselectivity of a similar reaction of **39**, since the resulting absolute axial chirality is consistent with the known absolute stereochemistry of the final product of the sequence, **61**.

The remarkable and useful consequence of the dynamic resolution is that it allows a simple two-step aminal formation–hydrolysis sequence to generate material of 62% ee from racemate in almost quantitative yield. We felt that 62% ee was insufficient for use as a chiral auxiliary, so we chose to work with the 99% ee material available by aqueous hydrolysis of purified **54a**. Losses on purification of the unstable aminal meant that the overall yield of this essentially enantiomerically pure material was, at 56%, just more than could be expected from a simple, non-dynamic resolution.

The diamine **52**, though recoverable, is made by a four-step sequence from proline.[63] Following some success with ephedrine **55** as an agent of dynamic thermodynamic resolution with atropisomeric amido-aldehydes,[67] we attempted a similar resolution with **42**. Unfortunately, the products **56a** and **56b** were formed in equal quantities, and after hydrolysis **42** was recovered with only 5% ee (Scheme 14).

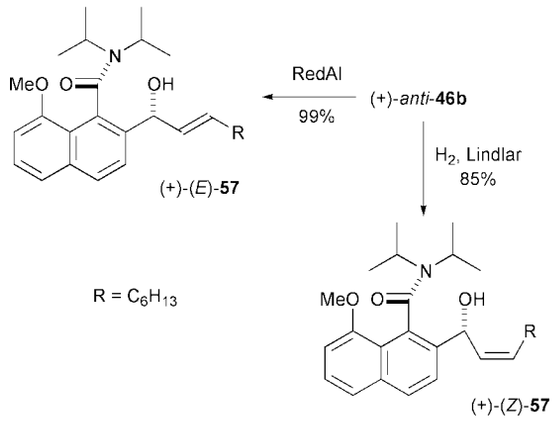
With enantiomerically pure (−)-**42** it was a straightforward matter to make enantiomerically pure alkyne (+)-*anti*-**46b**



Scheme 14 Attempted dynamic resolution with ephedrine.

using the catalytic Me_3Al method (Table 4, entry 8). For the auxiliary strategy, the alkyne required reduction to the allylic alcohols **57**, and we made both the *E*- and *Z*-isomers by reduction with RedAl or hydrogenation over Lindlar's catalyst (Scheme 15).

To recover the newly created stereogenic centre we decided to use two variants of the [3,3] sigmatropic Claisen rearrangement of known stereospecificity. Allylic alcohol (+)-(*Z*)-**57** was heated with trimethyl orthoacetate to give the ketene acetal **63** which underwent a stereospecific Johnson–Claisen rearrangement[68] in 12 h at 110 °C (Scheme 16). The product ester (+)-**64** was isolated as a single diastereoisomer in 84% yield. By



Scheme 15 Reduction to allylic alcohols **57** (R = *n*-hexyl).

contrast, Eschenmoser–Claisen rearrangement[69] of (+)-(*Z*)-**57** with dimethylacetamide dimethoxy acetal in refluxing xylene at 140 °C for 20 h gave a mixture of epimers of the product amide (+)-**59**. The most reasonable explanation for this is that the higher temperature allows equilibration of the atropisomeric epimers, particularly in the rearranged product which has a small,[41] trigonal substituent (a *trans* double bond) adjacent to the amide axis. The newly formed centre was nonetheless evidently formed with high stereospecificity, because ozonolysis of **59** with reductive work-up yielded an optically active alcohol (*R*)-(−)-**61** whose Mosher ester[70] **62** (formed from α-methoxy-α-(trifluoromethyl)phenylacetyl chloride, (+)-MTPACl) contained less than 5% of the diastereoisomer formed from the known[15] (*S*)-(+)-**61**. Fig. 2 compares the relevant portions of the ^{1}H NMR spectra of the (+)-MTPA esters of (*R*)-(−)-**61**, (*S*)-(+)-**61** and the (±)-MTPA ester of (*S*)-(+)-**61**.

Unfortunately, it proved impossible to recover the auxiliary (in its reduced form) from the ozonolysis step: the only other product turned out to be a benzamide **60** derived from further oxidation of the naphthalene's more electron-rich ring.

Although our route depends on resolution with naturally derived proline, and hence is not viable in the enantiomeric series, we demonstrated reduction to the (*E*)-, as well as the (*Z*)-, allylic alcohol **57**. Rearrangement chemistry from (*E*)-**57** should allow us to use the same strategy to make the enantiomeric series of alcohol products. A trial reaction on some racemic (±)-(*E*)-**59** suggested that the longer reaction times required to rearrange (*E*)-allylic alcohols would lead to epimerisation of the axis, preventing recovery of the auxiliary in enantiomerically pure form even if the problem of decomposition to **60** could be overcome. Other allylic alcohol rearrangements[71] (preferably ones which occur at lower temperatures) could be used to generate a variety of substituted allylic products: in our previous work with a phenylalanine-derived auxiliary[15] we demonstrated the use of a palladium(II)-catalysed allylic transposition of allyl esters.

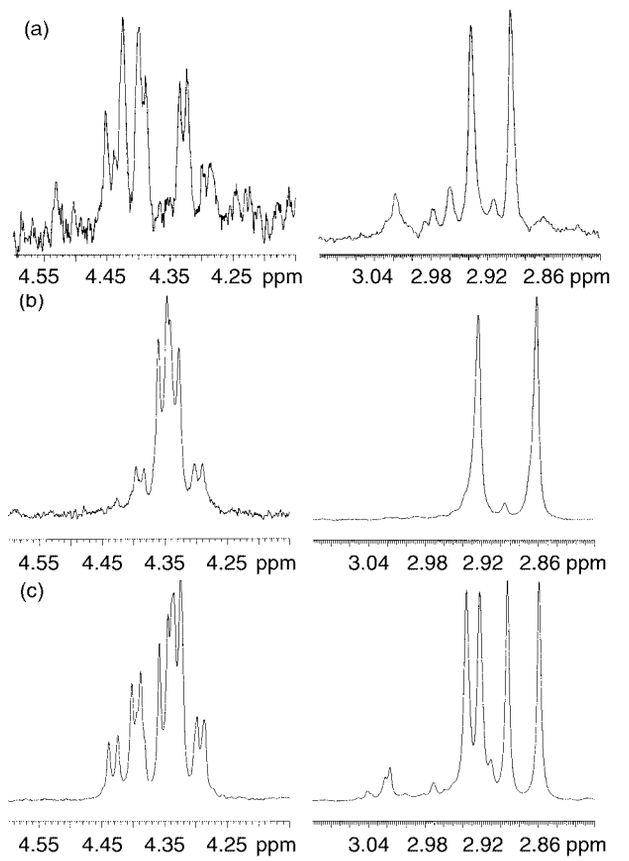
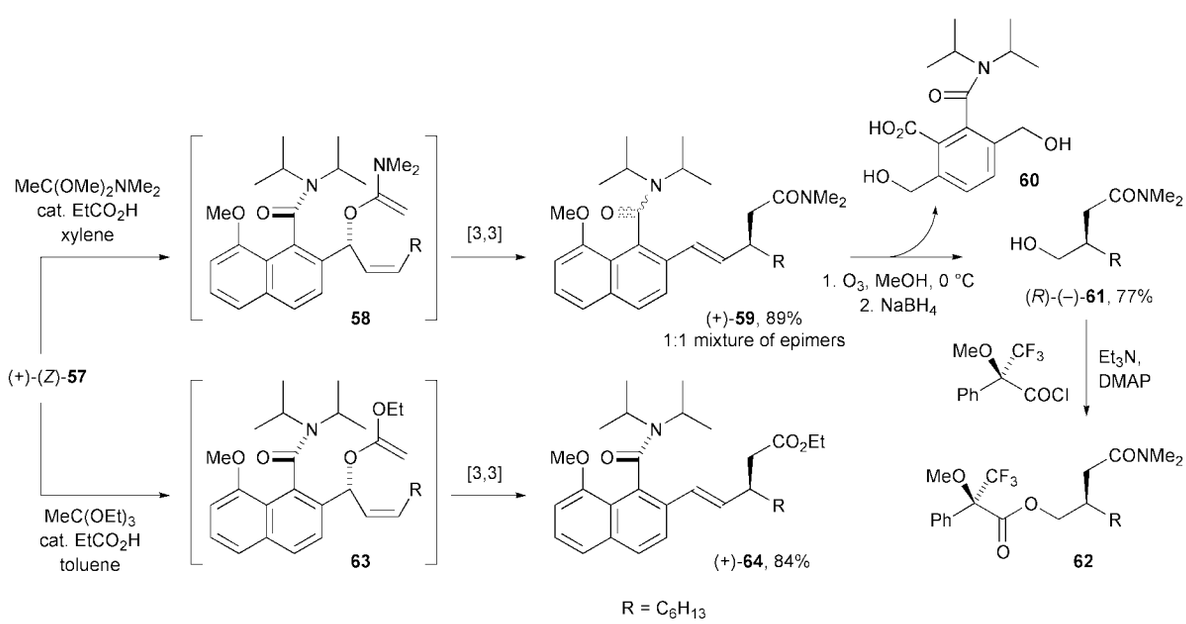


Fig. 2 (a) Portion of the ^{1}H NMR spectrum of **62**, the ester of (*R*)-(−)-**61** with (+)-MTPA; (b) portion of the ^{1}H NMR spectrum of the ester of (*S*)-(+)-**61** with (+)-MTPA (from ref. 15); (c) portion of the ^{1}H NMR spectrum of the ester of (*S*)-(+)-**61** with (±)-MTPA (from ref. 15).



Scheme 16 Stereospecific rearrangements and cleavage (R = *n*-hexyl).

Summary

The instability of amide-substituted phenyl esters poses severe problems for the use of atropisomeric amides as chiral auxiliaries in a conventional sense—enolate chemistry of the esters is made very difficult. However, allowing the new stereogenic centre to be formed by nucleophilic attack adjacent to the aromatic ring allows a way round this problem, albeit at the expense of a rather long synthetic sequence. Atropisomeric auxiliaries have some nice features—not least their potential for synthesis *via* dynamic resolution—but are evidently not a realistic competitive alternative to the more widely used and versatile alternatives.

Experimental

Flash chromatography refers to chromatography carried out by the method of Still *et al.*[72] 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}. Analytical HPLC on a chiral stationary phase was carried out using a Regis Whelk-O1 chiral column. Detection was at 280 nm using a Gilson 115 UV Detector. Ether refers to diethyl ether; petrol to the fraction of petroleum ether boiling between 40 and 60 °C. *J* values are in Hz.

Further experimental details are available as electronic supplementary information.

Phenyl *N*,*N*-diisopropylcarbamate 12a[73]

A solution of phenol (2.586 g, 27.47 mmol), *N*,*N*-diisopropylcarbamoyl chloride (4.496 g, 27.47 mmol) and anhydrous pyridine (10 ml) was heated to reflux for 2 days. The mixture was allowed to cool, poured onto ice-cooled water (50 ml) and extracted with ether (4 × 40 ml). The combined ethereal extracts were washed with aqueous 1 M hydrochloric acid (4 × 20 ml) and saturated aqueous sodium hydrogen carbonate (4 × 20 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude carbamate. Purification by Kugelrohr distillation yielded the carbamate **12a**[73] as a colourless liquid (5.599 g, 92%) which crystallised on standing, bp 150–155 °C, 2.1 mmHg; ν_{max} (film)/cm^{-1} 2996, 2971, 2935, 2876, 1710, 1692; δ_H(300 MHz, $CDCl_3$) 7.41 (2H, m, ArH), 7.23 (1H, m, ArH), 7.18 (2H, m, ArH), 4.15 (1H, br m, NCH), 4.03 (1H, br m, NCH), 1.38 (12H, br m, 4 × CH_3); δ_C(75 MHz, $CDCl_3$) 153.9, 151.3, 129.1, 124.9, 121.8, 46.8 (br), 21.5 (br), 20.5 (br); *m*/*z* (CI) 222 (100%, M + H^+); *m*/*z* (EI) 221 (2%, M^+) and 86 (100).

4-Hydroxyphenyl *N*,*N*-diisopropylcarbamate 12g

In the same way, a solution of hydroquinone **11g** (3.124 g, 28.37 mmol), *N*,*N*-diisopropylcarbamoyl chloride (4.643 g, 28.37 mmol) and anhydrous pyridine (10 ml) gave *carbamate* **12g** (5.908 g, 88%) as a white solid which required no further purification, mp 141–145 °C (EtOAc); R_f 0.23 [5:1 petrol–EtOAc]; λ_{max}/nm (ε_{max}) (CH_2Cl_2) 230 (10630), 278 (5234); ν_{max} (film)/cm^{-1} 3287, 3277, 2970, 2934, 2874, 1672; δ_H(300 MHz, $CDCl_3$) 7.35 (1H, br s, OH), 6.84 (2H, d, *J* 8.8, ArH), 6.58 (2H, d, *J* 8.9, ArH), 4.18 (1H, br m, NCH), 3.96 (1H, br m, NCH), 1.34 (12H, br m, 4 × CH_3); δ_C(75 MHz, $CDCl_3$) 153.8, 148.1, 143.8, 122.3, 116.3, 47.0, 46.0, 21.3, 20.4; *m*/*z* (CI) 238 (100%, M + H^+) (Found: M^+, 237.1362. $C_{13}H_{19}NO_3$ requires *M*, 237.1365).

4-(Methoxymethoxy)phenyl *N*,*N*-diisopropylcarbamate 12i

Sodium hydride (0.707 g, 17.67 mmol, 60% dispersion) was added in portions to a solution of carbamate **12g** (3.807 g, 16.06 mmol) in THF (210 ml) at 0 °C and stirred for 2 hours 45 minutes to give a deep blue mixture. Chloromethyl methyl ether (1.34 ml, 17.67 mmol) was added dropwise. The mixture was warmed to ambient temperature and stirred overnight. The white precipitate was filtered off and the solvent removed under reduced pressure. The crude solid was dissolved in ether (50 ml) and washed with water (50 ml), 10% aqueous sodium hydroxide (2 × 50 ml) and water (50 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give *carbamate* **12i** (4.185 g, 93%) as a white solid which required no further purification, mp 49–51 °C; R_f 0.23 [5:1 petrol–EtOAc]; λ_{max}/nm (ε_{max}) (CH_2Cl_2) 230 (24430), 276 (9486); ν_{max} (film)/cm^{-1} 2969, 2932, 1712; δ_H(300 MHz, $CDCl_3$) 7.06 (4H, s, ArH), 5.17 (2H, s, CH_2), 4.10 (2H, br m, 2 × NCH), 3.50 (3H, s, OCH_3), 1.35 (12H, br m, 4 × NCHCH_3); δ_C(75 MHz, $CDCl_3$) 154.3, 145.8, 122.6, 122.3, 116.8, 94.7, 55.7, 46.8, 46.0, 21.4, 20.5; *m*/*z* (CI) 282 (100%, M + H^+); *m*/*z* (EI) 281 (4%, M^+), 128 (53, CON*i*-Pr_2) and 45 (100) (Found: M^+, 281.1634. $C_{15}H_{23}NO_4$ requires *M*, 281.1627).

N,*N*-Diisopropyl-2-hydroxybenzamide 13a[73]

sec-Butyllithium (1.84 ml, 2.39 mmol; 1.3 M solution in hexanes) was added dropwise over 10 minutes to a solution of carbamate **12a** (528 mg, 2.39 mmol) in THF (36 ml) at −78 °C under an atmosphere of nitrogen. After 1 h, the resulting solution was warmed to ambient temperature, stirred for a further 12 hours and quenched with saturated aqueous ammonium chloride (10 ml). The THF was removed under reduced pressure and 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 the benzamide **13a**[73] (495 mg, 94%) as white needles which required no further purification, mp 159–160 °C (EtOAc); ν_{max} (film)/cm^{-1} 3206, 2998, 2969, 2934, 1611, 1590; δ_H(300 MHz, $CDCl_3$) 9.28 (1H, br s, OH), 7.32 (1H, m, ArH), 7.22 (1H, dd, *J* 7.7 and 1.7, ArH), 7.03 (1H, dd, *J* 8.2 and 1.1, ArH), 6.88 (1H, dt, *J* 7.5 and 1.1, ArH), 3.99 (2H, br m, 2 × NCH), 1.43 (12H, d, *J* 6.7, 4 × CH_3); δ_C(75 MHz, $CDCl_3$) 170.9, 157.7, 131.4, 126.6, 120.5, 118.5, 117.8, 48.9, 20.9; *m*/*z* (CI) 222 (100%, M + H^+); *m*/*z* (EI) 221 (100%, M^+), 178 (65, M − *i*-Pr) and 121 (88, M − N*i*-Pr_2).

N,*N*-Diisopropyl-2-hydroxy-5-(methoxymethoxy)benzamide 13i

By the method used for **13a**, a mixture of carbamate **12i** (2.283 g, 8.13 mmol) and *sec*-butyllithium (7.50 ml, 9.75 mmol; 1.3 M solution in hexanes) in THF (60 ml) gave, after flash chromatography on silica gel [3:2 petrol–EtOAc], *benzamide* **13i** (1.330 g, 58%) as white blades, mp 160–161 °C (EtOAc); ν_{max} (film)/cm^{-1} 3215–3101, 2996, 2965, 2935, 1589; δ_H(300 MHz, $CDCl_3$) 8.70 (1H, s, OH), 7.01 (1H, dd, *J* 8.8 and 2.9, ArH), 6.95 (1H, d, *J* 2.6, ArH), 6.92 (1H, d, *J* 9.2, ArH), 5.10 (2H, s, CH_2), 3.97 (2H, br m, 2 × NCH), 3.50 (3H, s, OCH_3), 1.42 (12H, d, *J* 6.7, 4 × NCHCH_3); δ_C(75 MHz, $CDCl_3$) 170.5, 152.4, 149.4, 120.4, 118.5, 114.6, 95.5, 55.7, 20.9; *m*/*z* (CI) 282 (100%, M + H^+); *m*/*z* (EI) 281 (7%, M^+) and 49 (100) (Found: M^+, 281.1623. $C_{15}H_{23}NO_4$ requires *M*, 281.1627).

2-(Diisopropylcarbamoyl)phenyl propionate 14a

n-Butyllithium (1.31 ml, 2.09 mmol; 1.6 M solution in hexanes) was added to a solution of benzamide **13a** (462 mg, 2.09 mmol) in THF (5.5 ml) at 0 °C under an atmosphere of nitrogen. After 10 minutes propionyl chloride (0.27 ml, 3.14 mmol) was added, and the mixture was allowed to warm to ambient temperature, stirred overnight, quenched with saturated aqueous ammonium chloride (10 ml) and extracted with ether (4 × 15 ml). The combined ethereal extracts were washed with saturated aqueous sodium hydrogen carbonate (3 × 10 ml) and brine (20 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the crude product. Purification by flash chromatography on silica gel [2:1 petrol–EtOAc] afforded the *ester* **14a** (549 mg, 95%) as a pale yellow oil, which crystal-

lised on standing; R_f 0.44 [2:1 petrol–EtOAc]; λ_{max}/nm (ε_{max}) (CH_2Cl_2) 232 (24530), 294 (1577); ν_{max} (film)/cm^{-1} 3062, 2985, 2929, 2882, 1764, 1633; δ_H(300 MHz, $CDCl_3$) 7.42–7.33 (2H, m, ArH), 7.24 (1H, m, ArH), 7.17 (1H, d, *J* 8.1, ArH), 3.77 (1H, septet, *J* 6.7, NCH), 3.50 (1H, septet, *J* 6.7, NCH), 2.57 (2H, q, *J* 7.6, CH_2), 1.54 (6H, m, 2 × NCHCH_3), 1.24 (3H, t, *J* 7.6, CH_2CH_3), 1.12 (6H, br d, 2 × NCHCH_3); δ_C(75 MHz, $CDCl_3$) 172.3, 166.8, 146.6, 131.6, 129.2, 126.2, 125.7, 123.0, 50.8, 45.7, 27.4, 20.7, 20.4, 8.9; *m/z* (CI) 278 (100%, M + H$^+$); *m/z* (EI) 277 (17%, M$^+$), 221 (77, M − C_3H_5O), 178 (78) and 121 (100) (Found: M$^+$, 277.1681. $C_{16}H_{23}NO_3$ requires *M*, 277.1678).

2-(Diisopropylcarbamoyl)-4-(methoxymethoxy)phenyl propionate 14i

In the same way as for compound **14a**, a mixture of benzamide **13i** (1.330 g, 4.73 mmol) and *n*-butyllithium (3.55 ml, 5.68 mmol; 1.6 M solution in hexanes) in THF (60 ml) was treated with propionyl chloride (0.62 ml, 7.10 mmol). After work-up in the usual manner, flash chromatography on silica gel [2:1 petrol–EtOAc] afforded the *ester* **14i** (1.487 g, 93%) as a colourless oil; R_f 0.48 [1:1 petrol–EtOAc]; ν_{max} (film)/cm^{-1} 2968, 2938, 1760, 1637; δ_H(300 MHz, $CDCl_3$) 7.15 (1H, d, *J* 8.9, ArH), 7.00 (1H, d, *J* 2.8, ArH), 6.88 (1H, d, *J* 2.6, ArH), 5.15 (1H, d, *J* 6.7, OCH_AH$_B$OCH$_3$), 5.08 (1H, d, *J* 6.7, OCH$_A$$H_BOCH_3$), 3.77 (1H, septet, *J* 6.7, NCH), 3.45 (1H, septet, NCH), 3.35 (3H, s, OCH_3), 2.51 (2H, q, *J* 6.7, CH_3CH_2), 1.49 (6H, br m, 2 × NCHCH_3), 1.19 (3H, t, *J* 7.4, CH_3CH$_2$), 1.09 (6H, d, *J* 6.6, 2 × NCHCH_3); δ_C(75 MHz, $CDCl_3$) 172.6, 166.4, 154.6, 140.8, 132.2, 123.8, 116.8, 113.7, 94.6, 55.8, 50.8, 45.7, 27.3, 20.6, 20.3, 8.8; *m/z* (CI) 338 (100%, M + H$^+$); *m/z* (EI) 281 (82%), 337 (3, M$^+$) and 45 (100) (Found: M$^+$, 337.1896. $C_{18}H_{27}NO_5$ requires *M*, 337.1889).

2-(Diisopropylcarbamoyl)-4-hydroxyphenyl propionate 14g

Concentrated hydrochloric acid (one drop) was added to a stirred solution of ester **14i** (1.487 g, 4.41 mmol) and sodium iodide (1.981 mg, 13.24 mmol) in acetone (30 ml) at ambient temperature. The pale green solution was stirred for 30 minutes, by which time it had turned red–brown. The mixture was heated to 50 °C for 4 hours, cooled to ambient temperature, treated with water (5 ml) and extracted with dichloromethane (4 × 10 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude product as a brown oil. Purification by flash chromatography on silica gel [2:1 petrol–EtOAc] afforded the *ester* **14g** (533 mg, 41%) as a sticky pale brown solid; R_f 0.21 [1:1 petrol–EtOAc]; ν_{max} (film)/cm^{-1} 3223, 2972, 2939, 2881, 1759, 1612; δ_H(300 MHz, $CDCl_3$) 8.90 (1H, br s, OH), 6.88 (1H, *J* 8.8, ArH), 6.68 (1H, dd, *J* 8.7 and 2.6, ArH), 6.56 (1H, d, *J* 2.6, ArH), 3.84 (1H, septet, *J* 6.6, NCH), 3.52 (1H, septet, *J* 6.6, NCH), 2.52 (2H, q, *J* 7.6, CH_2), 1.54 (6H, br m, 2 × NCHCH_3), 1.22 (3H, t, *J* 7.6, CH_3CH$_2$), 1.10 (6H, br m, 2 × NCHCH_3); δ_C(75 MHz, $CDCl_3$) 172.9, 168.1, 154.6, 138.8, 130.5, 123.5, 117.2, 113.1, 51.2, 45.9, 27.3, 20.5, 20.3, 8.9; *m/z* (CI) 294 (100%, M + H$^+$) (Found: M$^+$, 293.1628. $C_{16}H_{23}NO_4$ requires *M*, 293.1627).

4-Methoxy-2-methylphenyl *N*,*N*-diisopropylcarbamate 21a

sec-Butyllithium (2.07 ml, 2.69 mmol; 1.3 M solution in hexanes) was added dropwise to a solution of TMEDA (0.41 ml, 2.69 mmol) in THF (20 ml) at −78 °C under an atmosphere of nitrogen. After 10 minutes a solution of carbamate **12e** (562 mg, 2.24 mmol) in THF (10 ml) was added. After 1 h, methyl iodide (0.70 ml, 11.24 mmol) was added. The mixture was stirred for a further 60 minutes and allowed to warm to ambient temperature. Water (10 ml) was added, the THF was removed under reduced pressure, and 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 *carbamate* **21a** (568 mg, 96%) as a colourless oil which required no further purification; R_f 0.53 [2:1 petrol–EtOAc]; ν_{max} (film)/cm^{-1} 2996, 2969, 2934, 2876, 2836, 1712; δ_H(300 MHz, $CDCl_3$) 6.98 (1H, d, *J* 8.7, ArH), 6.78 (1H, d, *J* 2.9, ArH), 6.74 (1H, dd, *J* 8.7 and 3.0, ArH), 4.08 (2H, br m, 2 × NCH), 3.81 (3H, s, OCH_3), 2.23 (3H, s, $ArCH_3$), 1.35 (12H, br m, 4 × NCHCH_3); δ_C(75 MHz, $CDCl_3$) 156.7, 153.8, 143.5, 131.5, 122.8, 116.0, 111.6, 55.5, 46.6, 46.1, 21.5, 20.5, 16.7, 16.6; *m/z* (CI) 266 (100%, M + H$^+$), 128 (18, CON*i*-Pr$_2$); EI 265 (9, M$^+$), 86 (100) (Found: M$^+$, 265.1675. $C_{15}H_{23}NO_3$ requires *M*, 265.1678).

4-Methoxy-2-(trideuteriomethyl)phenyl *N*,*N*-diisopropylcarbamate 21c

In a similar way, a mixture of carbamate **12e** (800 mg, 3.19 mmol) in THF (10 ml) was added to a solution of *sec*-butyllithium (2.70 ml, 3.51 mmol; 1.3 M solution in hexanes) and TMEDA (0.53 ml, 3.51 mmol) in THF (20 ml) and treated with methyl iodide-d_3 (0.40 ml, 6.38 mmol). Work-up in the usual manner afforded *carbamate* **21c** (737 mg, 86%) as a colourless oil which required no further purification; R_f 0.50 [2:1 petrol–EtOAc]; ν_{max} (film)/cm^{-1} 2997, 2970, 2936, 2875, 2836; δ_H(300 MHz, $CDCl_3$) 6.99 (1H, d, *J* 8.7, ArH), 6.79 (1H, d, *J* 2.9, ArH), 6.76 (1H, dd, *J* 8.7 and 3.0, ArH), 4.08 (2H, br m, 2 × NCH), 3.81 (3H, s, OMe), 1.37 (12H, br m, 4 × NCHCH_3); δ_C(75 MHz, $CDCl_3$) 156.7, 153.8, 143.6, 131.4, 122.8, 122.6, 116.0, 114.2, 111.6, 55.4, 46.6, 46.1, 21.5, 20.5; *m/z* (CI) 269 (100%, M + H$^+$); *m/z* (EI) 268 (4%, M$^+$), 86 (100) (Found: M$^+$, 268.1860. $C_{15}H_{20}NO_3D_3$ requires *M*, 268.1866).

4-Methoxy-2-(trimethylsilyl)phenyl *N*,*N*-diisopropylcarbamate 21d

In the same way, a mixture of carbamate **12e** (872 mg, 3.47 mmol) in THF (10 ml) was added to a solution of *sec*-butyllithium (3.21 ml, 4.17 mmol; 1.3 M solution in hexanes) and TMEDA (0.63 ml, 4.17 mmol) in THF (20 ml) and treated with chlorotrimethylsilane (1.0 ml, 7.88 mmol). Work-up in the usual manner followed by flash chromatography on silica gel [8:1 petrol–EtOAc] afforded *carbamate* **21d** (789 mg, 70%) as a sticky white solid; R_f 0.30 [8:1 petrol–EtOAc]; λ_{max}/nm (ε_{max}) (CH_2Cl_2) 232 (29980), 282 (5976); ν_{max} (film)/cm^{-1} 2996, 2964, 2938, 2899, 1712; δ_H(300 MHz, $CDCl_3$) 6.96 (1H, d, *J* 2.9, ArH), 6.92 (1H, d, *J* 8.8, ArH), 6.87 (1H, dd, *J* 8.8 and 2.9, ArH), 4.34 (1H, septet, *J* 6.9, NCH), 3.78 (3H, s, OCH_3), 3.69 (1H, septet, *J* 6.7, NCH), 1.33 (6H, d, *J* 6.9, 2 × NCHCH_3), 1.28 (6H, d, *J* 6.7, 2 × NCHCH_3), 0.27 (9H, s, $Si(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 156.2, 153.5, 149.6, 132.9, 123.2, 119.9, 115.0, 55.5, 46.9, 45.8, 21.2, 20.5, 1.0; *m/z* (CI) 324 (100%, M + H$^+$), 128 (28, CON*i*-Pr$_2$); *m/z* (EI) 323 (3%, M$^+$), 128 (72, CON*i*-Pr$_2$), 86 (100) (Found: M$^+$, 323.1920. $C_{17}H_{29}NO_3Si$ requires *M*, 323.1917).

N,*N*-Diisopropyl-2-hydroxy-5-methoxy-3-methylbenzamide 22a

By a method similar to that used for **13a**, a solution of carbamate **21a** (530 mg, 2.00 mmol) in THF (10 ml) was added to a solution of *sec*-butyllithium (1.54 ml, 2.00 mmol; 1.3 M solution in hexanes) and TMEDA (0.30 ml, 2.00 mmol) in THF (20 ml), allowed to warm to ambient temperature and stirred overnight. After work-up in the usual manner, purification by flash chromatography on silica gel [5:1 petrol–EtOAc] afforded the *benzamide* **22a** (94 mg, 18%) as a colourless oil, λ_{max}/nm (ε_{max}) (CH_2Cl_2) 232 (14470), 318 (5533); ν_{max} (film)/cm^{-1} 3108, 2968, 2934, 1601; δ_H(300 MHz, $CDCl_3$) 8.52 (1H, s, OH), 6.79 (1H, d, *J* 3.0, ArH), 6.58 (1H, d, *J* 2.9, ArH), 3.98 (2H, br m, 2 × NCH), 3.78 (3H, s, OCH_3), 2.38 (3H, s, $ArCH_3$), 1.42 (12H, d, *J* 6.7, 4 × NCHCH_3); δ_C (75 MHz, $CDCl_3$) 171.0, 151.2, 149.5, 128.0, 120.3, 118.7, 108.7, 55.7, 48.9, 20.9, 16.2; *m/z* (CI)

266 (100%, M + H$^+$); *m*/*z* (EI) 265 (21%, M$^+$), 49 (100) (Found: M$^+$, 265.1674. $C_{15}H_{23}NO_3$ requires *M*, 265.1678).

Also obtained was *N*,*N*-diisopropyl-2-(2-hydroxy-5-methoxyphenyl)acetamide **23a** (140 mg, 26%) as a white solid; mp 154–156 °C (EtOAc); λ_{max}/nm (ε_{max}) (CH_2Cl_2) 232 (21458), 296 (12870); ν_{max} (film)/cm^{-1} 2963, 2932, 1613, 1596; δ_H(300 MHz, $CDCl_3$) 6.91 (1H, d, *J* 8.7, ArH), 6.75 (1H, dd, *J* 8.7 and 2.8, ArH), 6.61 (1H, d, *J* 2.8, ArH), 4.24 (1H, br septet, *J* 6.3, NCH), 3.76 (3H, s, OMe), 3.70 (2H, s, CH_2), 3.63 (1H, m, NCH), 1.36 (6H, d, *J* 6.7, 2 × NCHCH_3), 1.27 (6H, d, *J* 6.7, 2 × NCHCH_3); δ_C(75 MHz, $CDCl_3$) 172.1, 152.9, 150.9, 122.2, 118.2, 116.0, 113.2, 55.7, 46.5, 38.7, 21.1, 20.9, 20.3; *m*/*z* (CI) 266 (100%, M + H$^+$); *m*/*z* (EI) 265 (8%, M$^+$), 86 (100) (Found: M$^+$, 265.1679. $C_{15}H_{23}NO_3$ requires *M*, 265.1678). Also obtained was recovered carbamate **21a** (127 mg, 24%).

N,*N*-Diisopropyl-2-hydroxy-5-methoxy-3-(trideuteriomethyl)-benzamide 22c

In a similar way, a solution of carbamate **21c** (629 mg, 2.35 mmol) in THF (10 ml), *sec*-butyllithium (1.81 ml, 2.35 mmol; 1.3 M solution in hexanes) and TMEDA (0.35 ml, 2.35 mmol) in THF (20 ml) gave, after flash chromatography on silica gel [4:1 petrol–EtOAc], the *benzamide* **22c** (542 mg, 86%) as a white solid, mp 112–114 °C (EtOAc); R_f 0.53 [2:1 petrol–EtOAc]; ν_{max} (film)/cm^{-1} 3066, 2996, 2969, 2937, 2836, 1599; δ_H(300 MHz, $CDCl_3$) 8.55 (1H, s, OH), 6.79 (1H, d, *J* 3.0, ArH), 6.57 (1H, *J* 3.0, ArH), 3.97 (2H, br m, 2 × NCH), 3.78 (3H, s, OCH_3), 1.42 (12H, d, *J* 6.7, 4 × NCHCH_3); δ_C(75 MHz, $CDCl_3$) 171.0, 151.2, 149.5, 120.3, 118.7, 108.7, 55.7, 48.8, 20.9; *m*/*z* (CI) 269 (100%, M + H$^+$); *m*/*z* (EI) 268 (21%, M$^+$), 167 (100) (Found: M$^+$, 268.1863, $C_{15}H_{20}NO_3D_3$ requires *M*, 268.1866).

N,*N*-Diisopropyl-2-hydroxy-5-methoxy-3-(trimethylsilyl)-benzamide 22d

In the same way, a solution of carbamate **21d** (716 mg, 2.22 mmol) in THF (10 ml), *sec*-butyllithium (1.71 ml, 2.22 mmol; 1.3 M solution in hexanes) and TMEDA (0.33 ml, 2.22 mmol) in THF (20 ml) gave, after flash chromatograhy on silica gel [2:1 petrol–EtOAc], *benzamide* **22d** (694 mg, 97%) as a pale yellow oil; λ_{max}/nm (ε_{max}) (CH_2Cl_2) 234 (28412), 322 (12312); ν_{max} (film)/cm^{-1} 3240, 2996, 2964, 2902, 1612, 1584; δ_H(300 MHz, $CDCl_3$) 8.73 (1H, s, OH), 6.98 (1H, d, *J* 3.0, ArH), 6.70 (1H, d, *J* 3.0, ArH), 3.95 (2H, br m, 2 × NCH), 3.76 (3H, s, OCH_3), 1.40 (12H, d, *J* 6.7, 4 × NCHCH_3), 0.30 (9H, s, $Si(CH_3)_3$); δ_C(75 MHz, $CDCl_3$) 171.2, 156.3, 151.2, 129.7, 123.1, 119.3, 112.3, 55.8, 48.9, 20.9, 1.2; *m*/*z* (CI) 324 (100%, M + H$^+$); *m*/*z* (EI) 323 (23%, M$^+$), 207 (100) (Found: M$^+$, 323.1921. $C_{17}H_{29}NO_3Si$ requires *M*, 323.1917).

N,*N*-Diisopropyl-2-hydroxy-5-(methoxymethoxy)-3-(trimethylsilyl)benzamide 22e

In the same way, a solution of carbamate **21e** (813 mg, 2.30 mmol) in THF (15 ml), *sec*-butyllithium (2.13 ml, 2.76 mmol; 1.3 M solution in hexanes) and TMEDA (0.42 ml, 2.76 mmol) in THF (30 ml) gave, after purification by flash chromatography on silica gel [10:1 petrol–EtOAc], *benzamide* **22e** (669 mg, 82%) as a pale yellow oil; R_f 0.42 [5:1 petrol–EtOAc]; ν_{max} (film)/cm^{-1} 3224, 2967, 2936, 2899, 1612, 1581; δ_H(300 MHz, $CDCl_3$) 9.07 (1H, s, OH), 7.08 (1H, d, *J* 2.9, ArH), 6.96 (1H, d, *J* 2.9, ArH), 5.06 (2H, s, CH_2), 3.95 (2H, br m, 2 × NCH), 3.47 (3H, s, OCH_3), 1.39 (12H, d, *J* 6.6, 4 × NCHCH_3), 0.30 (9H, s, $Si(CH_3)_3$); δ_C(75 MHz, $CDCl_3$) 171.2, 157.6, 148.9, 129.7, 126.1, 118.9, 115.6, 95.6, 55.6, 48.8, 20.9, 1.2; *m*/*z* (CI) 354 (100%, M + H$^+$); *m*/*z* (EI) 353 (15%, M$^+$), 45 (100%) (Found: M$^+$, 353.2021. $C_{18}H_{31}NO_4Si$ requires *M*, 353.2022).

2-(Diisopropylcarbamoyl)-4-(methoxymethoxy)-6-(trimethylsilyl)phenyl propionate 25e

By the method used for **14a**, benzamide **22e** (167 mg, 0.47 mmol), *n*-butyllithium (0.33 ml, 0.52 mmol; 1.6 M solution in hexanes) in THF (7 ml) and propionyl chloride (0.06 ml, 0.71 mmol) gave, after flash chromatography on silica gel [5:1 petrol–EtOAc], *ester* **25e** (173 mg, 89%) as a colourless oil; R_f 0.73 [2:1 petrol–EtOAc]; ν_{max} (film)/cm^{-1} 2964, 2903, 1756, 1637; δ_H(300 MHz, $CDCl_3$) 7.07 (1H, d, *J* 3.0, ArH), 6.93 (1H, d, *J* 2.9, ArH), 5.16 (1H, *J* 6.7, OC*Ha*HbO), 5.07 (1H, d, *J* 6.7, OCHa*Hb*O), 3.90 (1H, septet, *J* 6.6, NCH), 3.44 (3H, s, OCH_3), 3.44 (1H, m, NCH), 2.52 (2H, m, CH_3CH_2), 1.49 (3H, d, *J* 7.3, NCHCH_3), 1.45 (3H, d, *J* 7.3, NCHCH_3), 1.19 (3H, t, *J* 7.6, CH_3CH_2), 1.13 (6H, d, *J* 6.5, 2 × NCHCH_3); δ_C(75 MHz, $CDCl_3$) 173.0, 166.9, 154.0, 146.2, 135.0, 132.0, 123.0, 114.8, 94.8, 55.8, 55.8, 50.9, 45.7, 27.5, 20.7, 20.3, 20.2, 8.7, 1.0; *m*/*z* (CI) 410 (65%, M + H$^+$), 74 (100) (Found: M + H$^+$, 410.2358. $C_{21}H_{35}NO_5Si$ requires *M* + H, 410.2362).

2-(Diisopropylcarbamoyl)-4-hydroxy-6-(trimethylsilyl)phenyl propionate 25f

By the method used to deprotect **14i**, ester **25e** (172 mg, 0.42 mmol) and sodium iodide (189 mg, 1.26 mmol) in acetone (5 ml) gave, after purification by flash chromatography on silica gel [6:1 petrol–EtOAc], *ester* **25f** (123 mg, 80%) as a white solid; mp 178–179 °C; R_f 0.24 [5:1 petrol–EtOAc]; λ_{max}/nm (ε_{max}) (CH_2Cl_2) 232 (24820), 292 (10790); ν_{max} (film)/cm^{-1} 3386–3192, 2944, 2935, 2870, 1756; δ_H(300 MHz, $CDCl_3$) 8.90 (1H, br s, OH), 6.77 (1H, d, *J* 2.8, ArH), 6.45 (1H, d, *J* 2.8, ArH), 3.93 (1H, septet, *J* 6.6, NCH), 3.46 (1H, septet, *J* 6.9, NCH), 2.49 (2H, m, CH_2), 1.51 (3H, d, *J* 7.0, NCHCH_3), 1.47 (3H, d, *J* 6.9, NCHCH_3), 1.19 (3H, t, *J* 7.6, CH_2CH_3), 1.13 (3H, d, *J* 6.5, NCHCH_3), 1.08 (3H, d, *J* 6.6, NCHCH_3), 0.20 (9H, s, $Si(CH_3)_3$); δ_C(75 MHz, $CDCl_3$) 173.2, 168.7, 153.7, 144.1, 134.2, 129.9, 123.2, 115.0, 51.3, 45.9, 27.6, 20.7, 20.2, 20.1, 8.8, 1.0; *m*/*z* (CI) 366 (100%, M + H$^+$); *m*/*z* (EI) 365 (M$^+$), 309 (83, M − C_3H_5O), 193 (100) (Found: C, 62.04; H, 8.61; N, 3.61%; M$^+$, 365.2022. $C_{19}H_{31}NO_4Si$ requires C, 62.4; H, 8.5; N, 3.8%; *M*, 365.2022).

General procedure for assessment of enolate stability

A solution of *n*-butyllithium (0.5 mmol; 1.6 M solution in hexanes) in THF (3 ml) at −78 °C was treated with diisopropylamine (0.075 ml, 0.55 mmol). After 10 min, a solution of the ester **14a** (0.5 mmol) in THF (2 ml) was added. After 60 minutes, saturated aqueous ammonium chloride (2 ml) was added. The mixture was allowed to warm to ambient temperature and extracted with dichloromethane (4 × 10 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the crude product, which was analysed by ^{1}H NMR. Table 2 shows the results for esters **14a**, **14c**, **14d**, **17**, **14g**, **25c** and **25f**.

(2*S**,3*S**)- and (2*R**,3*S**)-2-(Diisopropylcarbamoyl)-4-hydroxy-6-(trimethylsilyl)phenyl 3-hydroxy-2-methyl-3-phenylpropanoate, *syn*-26 and *anti*-26

n-Butyllithium (0.237 ml, 0.318 mmol; 1.6 M solution in hexanes) was added dropwise to a solution of diisopropylamine (0.045 ml, 0.32 mmol) in THF (1 ml) at 0 °C under nitrogen. After stirring for 10 minutes the solution was cooled to −78 °C and a solution of ester **25f** (58 mg, 0.16 mmol) in THF (2 ml) was added dropwise over 3 minutes to give a yellow solution. After 65 minutes, benzaldehyde (0.048 ml, 0.048 mmol) was added, the mixture was stirred for a further 2 hours 20 minutes, and saturated aqueous ammonium chloride (5 ml) was added dropwise to give a solution that turned green, then pale yellow, then colourless upon warming to ambient temperature. Water (5 ml) was added, and the mixture was extracted with dichloro-

methane (5 × 5 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give an oil. Purification by flash chromatography on silica gel [4:1 petrol–EtOAc] afforded the *syn aldol syn*-**26** (24 mg, 32%) as a colourless oil; R_f 0.52 [1:1 petrol–EtOAc]; ν_{max} (film)/cm^{-1} 3307–3215, 2967, 2938, 1754, 1606, 1581; δ_H(300 MHz, 90 °C, DMSO-d_6) 9.26 (1H, br s, ArOH), 7.67–7.20 (5H, m, Ph), 6.89 (1H, *J* 2.6, ArH), 6.63 (1H, d, *J* 2.8, ArH), 5.25 (1H, br s, OH), 4.89 (1H, br s, C*H*OH), 3.65 (2H, br m, 2 × NCH), 2.84 (1H, br m, PhCH(OH)C*H*CH$_3$), 1.25 (12H, br m, 4 × NCHC*H*$_3$), 1.07 (3H, d, *J* 7.0, PhCH(OH)CHC*H*$_3$), 0.20 (9H, s, Si(CH$_3$)$_3$); δ_C(75 MHz, CDCl$_3$) 177.6, 172.2, 159.3, 149.1, 148.7, 139.6, 136.9, 133.0, 131.8, 131.0, 126.5, 119.2, 76.9, 76.7, 52.0, 51.8, 25.5, 14.3, 4.7, 4.5, 4.2, 4.0; *m/z* (CI) 472 (100%, M + H$^+$); *m/z* (EI) 105 (100%), 309 (29, M − PhC$_4$H$_6$O$_2$) (Found: M + H$^+$, 472.2526. $C_{26}H_{37}NO_5Si$ requires *M* + H, 472.2519).

Also obtained was the *anti aldol anti*-**26** (31 mg, 41%) as a colourless oil; R_f 0.50 [1:1 petrol–EtOAc]; ν_{max} (film)/cm^{-1} 3306, 2969, 2936, 1749, 1607, 1580; δ_H(300 MHz, 90 °C, DMSO-d_6) 9.25 (1H, br s, ArOH), 7.37–7.22 (5H, m, Ph), 6.89 (1H, d, *J* 2.9, ArH), 6.62 (1H, d, *J* 2.9, ArH), 5.08 (1H, d, *J* 4.0, OH), 4.74 (1H, dd, *J* 8.2 and 3.8, C*H*OH), 3.61 (2H, br m, 2 × NCH), 2.85 (1H, quintet, *J* 7.3, PhCH(OH)C*H*(CH$_3$)), 1.3 (12H, br m, 4 × NCHC*H*$_3$), 0.91 (3H, d, *J* 7.3, PhCH(OH)-CH(C*H*$_3$)), 0.21 (9H, s, SiMe$_3$); δ_C(75 MHz, CDCl$_3$) 173.3, 154.3, 144.0, 142.9, 134.8, 132.2, 128.3, 127.5, 127.1, 121.9, 114.5, 114.3, 75.0, 47.7, 47.4, 20.5, 14.1, 13.8; *m/z* (CI) 472 (16%, M + H$^+$), 102 (100%) (Found: M + H$^+$, 472.2522. $C_{26}H_{37}NO_5Si$ requires *M* + H, 472.2519).

Also recovered was *N,N-diisopropyl-2,5-dihydroxy-3-(trimethylsilyl)benzamide* **22f** (5 mg, 13%) as a white solid; mp 182–185 °C (EtOAc); R_f 0.56 [1:1 petrol–EtOAc]; ν_{max} (film)/cm^{-1} 3258, 2961, 2925, 2872, 2854, 1586; δ_H(300 MHz, CDCl$_3$) 6.86 (1H, d, *J* 2.9, ArH), 6.62 (1H, *J* 3.09, ArH), 3.94 (2H, br m, 2 × NCH), 1.38 (12H, d, *J* 6.7, 4 × NCHC*H*$_3$), 0.29 (9H, s, Si(CH$_3$)$_3$); δ_C(75 MHz, CDCl$_3$) 170.9, 155.6, 147.2, 129.8, 123.9, 120.0, 114.1, 29.6, 20.9, −1.2; *m/z* (CI) 310 (100%, M + H$^+$); *m/z* (EI) 309 (3%, M$^+$), 49 (100) (Found: M$^+$, 309.1759. $C_{16}H_{27}NO_3Si$ requires *M*, 309.1760). Also recovered was ester **25f** (6 mg, 10%).

(2*S**,3*S**)- and (2*R**,3*S**)-2-(Diisopropylcarbamoyl)-4-hydroxyphenyl 3-hydroxy-2-methyl-3-phenylpropanoate *syn*- and *anti*-18

By the same method, a solution of LDA [from diisopropylamine (0.14 ml, 0.99 mmol) and *n*-butyllithium (0.64 ml, 0.99 mmol; 1.54 M solution in hexanes) in THF (30 ml)] at −78 °C was treated with a solution of ester **14g** (145 mg, 0.50 ml) in THF (25 ml). After 25 minutes, a solution of benzaldehyde (0.13 ml, 1.24 mmol) in THF (5 ml) was added and the mixture was stirred overnight. After work-up in the manner described above, purification by flash chromatography on silica gel [4:1 petrol–EtOAc] afforded a mixture of *aldol products syn*-**18** and *anti*-**18** (123 mg, 62%) as a colourless oil.

(1*R**,2*S**)-2-Methyl-1-phenylpropane-1,3-diol *syn*-20 by reduction of *syn*-26

A solution of ester *syn*-**26** (43 mg, 0.09 mmol) in THF (4 ml) was added to a stirred solution of lithium aluminium hydride (17 mg, 0.45 mmol) at 0 °C in THF (2 ml). The mixture was warmed to ambient temperature, stirred for 3 hours, heated to reflux overnight, allowed to cool and treated successively with water (0.5 ml), 15% aqueous sodium hydroxide (0.5 ml) and water (1.5 ml). The mixture was extracted with diethyl ether (3 × 10 ml), and the combined ethereal extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the crude product. Purification by flash chromatography on silica gel [5:1 petrol–EtOAc] afforded *2-(diisopropylaminomethyl)-6-(trimethylsilyl)benzene-1,4-diol* **27** (10 mg, 49%) as a sticky brown oil, ν_{max} (film)/cm^{-1} 3359, 2968, 2932, 2897, 2876, 2855; δ_H(300 MHz, CDCl$_3$) 6.45 (1H, s, ArH), 6.25 (1H, s, ArH), 5.03 (2H, d, *J* 1.9, CH$_2$), 2.86 (2H, septet, *J* 6.7, 2 × NCH), 0.83 (12H, d, *J* 6.5, N(CH(C*H*$_3$)$_2$)$_2$), 0.01 (9H, s, SiMe$_3$); δ_C(75 MHz, CDCl$_3$) 156.7, 148.1, 126.3, 122.5, 119.4, 116.7, 67.8, 47.6, 19.7, −1.1; *m/z* (CI) 296 (6%, M + H$^+$), 102 (100) (Found: M + H$^+$, 296.2043. $C_{16}H_{29}NO_2Si$ requires *M* + H, 296.2046).

Also obtained was the *diol syn*-**20** (17 mg, 100%) as a colourless oil.

Diols 20 by reduction of esters *syn*- and *anti*-18

In the same way lithium aluminium hydride (17 mg, 0.45 mmol) at 0 °C in THF (2 ml) and a solution of diastereoisomeric aldols **18** (123 mg, 0.308 mmol) in THF (4 ml) gave, after heating to reflux for 3 hours and after purification by flash chromatography on silica gel [2:1 petrol–EtOAc + 1% Et$_3$N], *2-(diisopropylcarbamoyl)benzene-1,4-diol* **19** (14 mg, 22%) as a sticky brown solid; ν_{max} (film)/cm^{-1} 3260, 2964, 2928, 2871, 2855, 2751, 2732; δ_H(300 MHz, CDCl$_3$) 6.59 (2H, s, ArH), 6.48 (1H, s, ArH), 3.74 (2H, s, CH$_2$), 3.12 (2H, septet, *J* 6.7, 2 × NCH), 1.10 (12H, d, *J* 6.6, N(CH(C*H*$_3$)$_2$)$_2$); δ_C(75 MHz, CDCl$_3$) 169.6, 151.7, 123.1, 116.0, 114.9, 114.5, 48.3, 47.6, 19.5; *m/z* (CI) 224 (72%, M + H$^+$), 102 (100%); *m/z* (EI) 223 (1%, M$^+$), 49 (100) (Found: M$^+$, 223.1568. $C_{13}H_{21}NO_2$ requires *M*, 223.1572).

Also obtained was a mixture of *(1S*,2S*)*- and *(1R*,2S*)-2-methyl-1-phenylpropane-1,3-diol syn*- and *anti*-**20** (10 mg, 20%) in a ratio of 69:31.

(2*R**,4*R**,5*S**)-5-Methyl-2,4-diphenyl-1,3-dioxane 28

A mixture of diol *syn*-**20** (17 mg, 0.10 mmol), benzaldehyde (0.5 ml, 4.9 mmol), toluene-*p*-sulfonic acid (a few crystals), 4 Å molecular sieves and toluene (2 ml) was heated to reflux overnight, cooled to ambient temperature, diluted with diethyl ether (15 ml), washed with saturated aqueous sodium hydrogen carbonate (2 × 10 ml) and brine (10 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the crude product. Purification by flash chromatography on neutral alumina [5:1 petrol–EtOAc] afforded *dioxane* **28** (26 mg, 100%) as a colourless oil; ν_{max} (film)/cm^{-1} 3305–2848, 1721; δ_H(300 MHz, CDCl$_3$) 7.54 (2H, dd, *J* 7.8 and 1.9, ArH), 7.38–7.16 (8H, m, ArH), 5.65 (1H, s, OC*H*OPh), 5.09 (1H, d, *J* 2.5, PhC*H*OCHCH$_3$), 4.25 (1H, dd, *J* 11.1 and 2.2, C*H*$_A$H$_B$), 4.07 (1H, dd, *J* 11.1 and 1.2, CH$_A$*H*$_B$), 1.87 (1H, m, C*H*CH$_3$), 0.90 (3H, d, *J* 7.0, CHC*H*$_3$); δ_C(75 MHz, CDCl$_3$) 128.8, 128.2, 128.0, 126.9, 126.1, 125.2, 101.9, 80.7, 73.3, 34.0, 11.2; *m/z* (CI) 255 (82%, M + H$^+$), 106 (100) (Found: M$^+$, 254.1302. $C_{17}H_{18}O_2$ requires *M*, 254.1307).

(*R**a,1′*R**)- and (*R**a,1′*S**)-*N*,*N*-Diisopropyl-8-(dimethylamino)-2-(1′-hydroxypentyl)-1-naphthamide *anti*-45a and *syn*-45a

The aldehyde **41** (0.2 g, 0.6 mmol) in THF (50 ml) was added to a stirred solution of *n*-butyllithium (0.38 ml; 1.6 M solution in hexane) in THF (50 mL) under nitrogen at −78 °C. After 30 min the mixture was warmed to room temperature for 30 min. Saturated NH_4Cl was added and the mixture was extracted with dichloromethane (2 × 60 ml). The extracts were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. Analytical HPLC of the crude mixture showed that the atropisomers were present in a ratio of 15.5 (*anti*):1 (*syn*). Purification by flash chromatography on SiO_2 [1:5 EtOAc–petrol] gave the *anti alcohol anti*-**45a** (0.12 g, 57%) as white plates, mp 124–128 °C; R_f [1:5 EtOAc–petrol] 0.37; ν_{max} (film)/cm^{-1} 3422 (O–H), 1628 (C=O); δ_H(300 MHz, CDCl$_3$) 7.86 (1H, d, *J* 8.5, ArH), 7.70 (1H, d, *J* 8.5, ArH), 7.60 (1H, d, *J* 8, ArH), 7.44 (1H, t, *J* 7.5, ArH), 7.28 (1H, d, *J* 7.5, ArH), 5.05 (1H, dt, *J* 3.5 and 9, *H*COH), 3.50 [1H, septet, *J* 6.5, NC*H*(CH$_3$)$_2$], 3.10 [1H, septet,

J 6.5, NC*H*$(CH_3)_2$], 2.84 (3H, s, NMe), 2.56 (3H, s, NMe), 1.98 (2H, d, *J* 4, OH), 1.66 (3H, d, *J* 7, NCHC*H*$_3$), 1.65 (3H, d, *J* 7, NCHC*H*$_3$), 1.60 [2H, m, C*H*$_2(CH_2)_2CH_3$], 1.50–1.30 [4H, m, $(CH_2)_2CH_3$], 0.94 (3H, d, *J* 7, NCHC*H*$_3$), 0.92 (3H, d, *J* 7, NCHC*H*$_3$), 0.94 (3H, t, *J* 7, CH_3); δ_C(75 MHz, $CDCl_3$) 169.1 (C=O), 152.1, 139.8, 134.4, 130.5, 128.8, 126.3, 125.9, 124.3, 123.8, 117.0 (ArC), 71.6 (COH), 50.6, 49.7 (NMe_2), 45.6, 43.8 (NCH × 2), 39.3 (HOCH*C*H$_2$), 28.4, 22.5 ((CH_2) × 2), 20.7, 20.4, 20.3, 19.6 (CH_3 × 4), 14.1 (CH_3); *m*/*z* (CI) 385 (100%, $(M + H)^+$), (EI) 183 (52), 86 (80, 2 × *i*-Pr) (Found (EI): M^+, 384.2787. $C_{24}H_{36}N_2O_2$ requires *M*, 384.2777).

Also obtained was the *syn alcohol syn*-**45a** as white plates; mp 125–128 °C; R_f [1 : 5 EtOAc–petrol] 0.25; ν_{max} (film)/cm^{-1} 1687 (C=O); δ_H(300 MHz, $CDCl_3$) 7.74 (1H, d, *J* 8.5, ArH), 7.53 (1H, d, *J* 8.5, ArH), 7.48 (1H, d, *J* 8, ArH), 7.33 (1H, t, *J* 7.5, ArH), 7.14 (1H, d, 7.5, ArH), 4.80 (1H, m, *H*COH), 3.94 (1H, s, OH), 3.43 [1H, septet, *J* 7, NC*H*$(CH_3)_2$], 2.95 (1H, septet, *J* 7, NC*H*$(CH_3)_2$), 2.74 (3H, s, NMe), 2.45 (3H, s, NMe), 1.80 (3H, d, *J* 7, NCHC*H*$_3$), 1.75 (3H, d, *J* 7, NCHC*H*$_3$), 1.35 [2H, m, C*H*$_2(CH_2)CH_3$], 1.30–1.10 [4H, m, $CH_2(CH_2)CH_3$], 0.80 (3H, d, *J* 7, NCHC*H*$_3$), 0.75 (3H, d, *J* 7, NCHC*H*$_3$), 0.80 (3H, m, CH_3); δ_C(75 MHz, $CDCl_3$) 170.9 (C=O), 151.6, 138.8, 134.2, 132.6, 128.8, 126.2, 125.9, 123.9, 123.30, 116.2 (ArC), 69.5 (C-OH), 50.4, 49.8 (NMe_2), 45.7, 43.3 (NCH × 2), 33.3, 29.4, 28.8 [$(CH_2)_3$], 22.6, 22.3, 20.2, 19.3 (4 × CH_3), 13.9 (CH_3); *m*/*z* (CI) 385 (100%, $(M + H)^+$), (EI) 86 (80, 2 × *i*-Pr) (Found (EI): M^+, 384.2783. $C_{24}H_{36}N_2O_2$ requires *M*, 384.2777).

(*R**a,1′*R**)-*N*,*N*-Diisopropyl-8-(dimethylaminomethyl)-2-(1′-hydroxynon-2′-ynyl)-1-naphthamide *anti*-44b

Method A. *n*-Butyllithium (0.83 ml; 1.6 M solution in hexane) was added dropwise to a stirred solution of oct-1-yne (0.20 ml, 1.3 mmol) in THF (30 ml) under nitrogen at 0 °C. After 30 min at 0 °C, the aldehyde **40** (0.3 g, 0.8 mmol) was added and the mixture was stirred for 30 min at −78 °C, 30 min at 0 °C and 30 min at room temperature. The mixture was poured into aqueous HCl (1 M, 30 ml) and extracted with dichloromethane (2 × 30 ml). The extracts were washed with sodium bicarbonate solution and brine, dried ($MgSO_4$) and evaporated under reduced pressure. Analytical HPLC of the crude mixture showed that the atropisomers were present in a ratio of 1 (*anti*) : 1 (*syn*). Purification by flash chromatography on SiO_2 (20 : 1 EtOAc–MeOH) gave the *anti alcohol anti*-**44b** (0.26 g, 66%) as a yellow oil; R_f (20 : 1 EtOAc–MeOH) 0.33; ν_{max} (film)/cm^{-1} 3357 (OH), 2931 (CH), 1624 (C=O); δ_H(300 MHz, $CDCl_3$) 7.94 (1H, d, *J* 7, ArH), 7.80 (1H, d, *J* 8, ArH), 7.65 (1H, d, *J* 8, ArH), 7.42 (1H, t, *J* 8, ArH), 7.40 (1H, d, *J* 8, ArH), 5.60 (1H, s, C*H*OH), 4.14 (1H, d, *J* 15.5, $Me_2NCH_AH_B$), 3.88 (1H, d, *J* 15.5, $Me_2NCH_AH_B$), 3.52 [1H, septet, *J* 7, NC*H*$(CH_3)_2$], 3.05 [1H, septet, *J* 7, NC*H*$(CH_3)_2$], 2.20 (6H, s, NMe_2), 1.60 (3H, d, *J* 7, NCHC*H*$_3$), 1.55 (3H, d, *J* 7, NCHC*H*$_3$), 1.50 [2H, m, C*H*$_2(CH_2)_4CH_3$], 1.40 [2H, m, $CH_2CH_2(CH_2)_3CH_3$], 1.20 [6H, m, $(CH_2)_3CH_3$], 0.90 (3H, d, *J* 7, NCHC*H*$_3$), 0.85 (3H, d, *J* 7, NCHC*H*$_3$), 0.85 (3H, t, *J* 7, CH_3); δ_C(75 MHz, $CDCl_3$) 170.0 (C=O), 138.3, 135.6, 134.2, 131.5, 130.2, 130.2, 127.8, 127.5, 126.3, 124.4 (ArH), 88.0 (COH), 80.1, 79.4 (alkyne C), 61.5 (Me_2NCH_2), 50.8 (NMe_2), 46.3, 45.6 (2 × NCH), 31.2, 28.4, 22.4, 20.3, 20.2 (5 × CH_2), 20.0, 19.8, 19.6, 18.8 (4 × CH_3), 13.9 (CH_3); *m*/*z* (CI) 451 (100%, $(M + H)^+$) (Found (EI): $(M + H)^+$, 451.3332. $C_{29}H_{42}N_2O_2$ requires *M*, 451.3246).

Method B. Alternatively, *n*-butyllithium (0.8 ml; 1.6 M solution in hexane) was added dropwise to a stirred solution of oct-1-yne (0.20 ml, 1.3 mmol) in THF (30 ml) under nitrogen at −78 °C. After 30 min at −78 °C, chlorotitanium triisopropoxide (0.34 g, 1.3 mmol) was added dropwise and the mixture warmed to 0 °C and stirred at this temperature for 45 min. The aldehyde **40** (0.3 g, 0.8 mmol) was added and the mixture was stirred for 6 h at 0 °C and room temperature for 30 min, poured into aqueous HCl (1 M, 30 ml) and extracted with dichloromethane (2 × 30 ml). The extracts were washed with sodium bicarbonate solution and brine, dried ($MgSO_4$) and evaporated under reduced pressure. Analytical HPLC of the crude mixture showed that the atropisomers were present in a ratio of 2 (*anti*) : 1 (*syn*). Purification by flash chromatography on SiO_2 (20 : 1 EtOAc–MeOH) gave the *anti alcohol anti*-**44b** (47 mg, 36%) as a yellow oil.

(*R**a,1′*R**) and (*R**a,1′*S**)-*N*,*N*-Diisopropyl-8-(dimethylamino)-2-[1′-hydroxynon-2′-ynyl]-1-naphthamide *anti*-45b and *syn*-45b

By method A, *n*-butyllithium (0.43 ml; 1.6 M solution in hexane), oct-1-yne (0.14 mL, 0.9 mmol) and aldehyde **41** (150 mg, 0.46 mmol) gave a crude product. Analytical HPLC of the crude mixture showed that the atropisomers were present in a ratio of 2 (*anti*) : 1 (*syn*). Purification by flash chromatography on SiO_2 (1 : 5 EtOAc–petrol) gave the *anti alcohol anti*-**45b** as a yellow oil (69 mg, 35%); R_f [1 : 5 EtOAc–petrol] 0.23; ν_{max} (film)/cm^{-1} 3388 (OH), 1627 (C=O); δ_H(300 MHz, $CDCl_3$) 7.74 (1H, d, *J* 8.5, ArH), 7.74 (1H, d, *J* 8.5, ArH), 7.46 (1H, d, *J* 8, ArH), 7.34 (1H, t, *J* 7.5, ArH), 7.14 (1H, d, *J* 7.5, ArH), 5.70 (1H, m, HCOH), 3.40 [1H, septet, *J* 7, NC*H*$(CH_3)_2$], 2.80 [1H, septet, *J* 7, NC*H*$(CH_3)_2$], 2.72 (3H, s, NMe), 2.66 (1H, d, *J* 5.5, OH), 2.46 (3H, s, NMe), 2.15 [2H, m, C*H*$_2(CH_2)_4CH_3$], 1.60 (3H, d, *J* 7, NCHC*H*$_3$), 1.55 (3H, d, *J* 7, NCHC*H*$_3$), 1.40–1.20 (8H, m, $(CH_2)_4$), 0.84 (3H, t, *J* 7, CH_3), 0.78 [3H, d, *J* 7, NCH$(CH_3)_2$]; δ_C(75 MHz, $CDCl_3$) 170.7 (C=O), 151.6, 136.9, 134.8, 131.6, 129.0, 126.4, 126.1, 125.9, 124.2, 116.7 (ArC), 88.0 (COH), 78.4, 62.4 (alkyne C), 50.5, 50.2 (NMe_2), 45.9, 43.5 (NCH × 2), 31.2, 28.5, 28.4, 22.4, 20.5 (5 × CH_2), 20.4, 20.2, 19.4, 18.8 (4 × CH_3), 13.9 (CH_3); *m*/*z* (CI) 437 (100%, $(M + H)^+$), (EI) 226 (52), 86 (30, 2 × *i*-Pr) (Found: $(M + H)^+$, 437.3176. $C_{28}H_{40}N_2O_2$ requires *M* + 1, 437.3168).

Also obtained was the *syn alcohol syn*-**45b** as a yellow oil (35 mg, 18%); R_f [1 : 5 EtOAc–petrol] 0.14; ν_{max} (film)/cm^{-1} 3388 (OH), 1627 (C=O); δ_H(300 MHz, $CDCl_3$) 8.00 (1H, d, *J* 8.5, ArH), 7.76 (1H, d, *J* 8.5, ArH), 7.50 (1H, d, *J* 8, ArH), 7.35 (1H, t, *J* 8, ArH), 7.16 (1H, d, *J* 7.5, ArH), 5.70 (1H, s, C*H*OH), 4.20 (1H, br, OH), 3.45 [1H, septet, *J* 7, NCH$(CH_3)_2$], 2.92 [1H, septet, *J* 7, NCH$(CH_3)_2$], 2.72 (3H, s, NMe), 2.42 (3H, s, NMe), 2.25 (2H, m, alkyne-CH_2), 1.62 (3H, d, *J* 7 NCHCH_3), 1.60 (3H, d, *J* 7, NCHC*H*$_3$), 1.35 (2H, m, CH_2), 1.40–1.10 [6H, m, $(CH_2)_3$], 0.85 (3H, t, *J* 7, CH_3), 0.80 (6H, d × 2, *J* 7, NCH$(CH_3)_2$); δ_C(75 MHz, $CDCl_3$) 170.7 (C=O), 151.6, 136.9, 134.8, 131.6, 129.0, 126.4, 126.1, 125.5, 124.2, 116.7 (ArC), 88.0 (COH), 78.4, 62.4 (alkyne C), 50.5, 50.2 (NMe_2), 45.9, 43.5 (NCH × 2), 31.2, 28.5, 28.4, 22.4, 20.5 (5 × CH_2), 20.4, 20.2, 19.4, 18.9 (4 × CH_3), 13.9 (CH_3); *m*/*z* (CI) 437 (40%, $(M + H)^+$), 419 (73), (EI) 226 (75), 210 (73) and 86 (47, 2 × *i*-Pr) (Found: $(M + H)^+$, 437.3173. $C_{28}H_{40}N_2O_2$ requires *M* + 1, 437.3168).

9-(Dimethylamino)-3-(oct-1-ynyl)-1,3-dihydronaphtho[1,2-*c*]-furan-1-one 47

By method B, *n*-butyllithium (0.43 ml; 1.6 M solution in hexane), oct-1-yne (0.14 m, 0.91 mmol), chlorotitanium triisopropoxide (0.30 ml; 1 M solution in hexane) and *aldehyde* **41** (150 mg, 0.46 mmol) gave, after purification by flash chromatography [1 : 6 EtOAc–petrol], the *lactone* **47** as a yellow oil (0.17 g, 83%); R_f [1 : 6 EtOAc–petrol] 0.2; δ_H(300 MHz, $CDCl_3$) 7.98 (1H, d, *J* 8, ArH), 7.80 (1H, d, *J* 8, ArH), 7.60 (1H, d, *J* 8, ArH), 7.45 (1H, d, *J* 7, ArH), 7.10 (1H, t, *J* 7, ArH), 5.90 (1H, s, COCH), 4.60 (1H, m, alkyne-CH_AH_B), 4.45 (1H, m, alkyne-CH_AH_B), 2.90 (3H, s, NMe), 2.85 (3H, s, NMe), 1.65 (2H, t, *J* 7, alkyne-CH_2CH_2), 1.28 (6H, m, $(CH_2)_2CH_3$), 0.90 (3H, m, CH_3).

(*Ra,1′*S**) and (*R**a,1′*R**)-*N*,*N*-Diisopropyl-2-(1′-hydroxynon-2′-ynyl)-8-methoxy-1-naphthamide *anti*-46b and *syn*-46b**

By method A, *n*-butyllithium (1.1 ml; 1.6 M solution in hexane), oct-1-yne (0.2 ml, 1.4 mmol) and *aldehyde* **42** (150 mg, 0.48 mmol) gave a crude product. Analytical HPLC of the crude mixture showed that the atropisomers were present in a ratio of 1 (*anti*):3 (*syn*). Purification by column chromatography [1:2 EtOAc–petrol], gave the *anti alcohol anti*-**46b** (14 mg, 7%) as a pale yellow oil; R_f [1:2 EtOAc–petrol] 0.56; δ_H(300 MHz, $CDCl_3$) 7.74 (2H, d × 2, *J* 8.5, ArH), 7.34 (1H, t, *J* 7, ArH), 7.30 (1H, d, *J* 8, ArH), 6.77 (1H, d, *J* 6.5, ArH), 5.60 (1H, s, HOC*H*), 3.80 (3H, s, OMe), 3.45 [1H, septet, *J* 7, NC*H*$(CH_3)_2$], 3.35 [1H, septet, *J* 7, NC*H*$(CH_3)_2$], 2.6 (1H, br, OH), 2.10 (CH_2, m, alkyne-CH_2), 1.60 (3H, d, *J* 7, NCHCH_3), 1.55 (3H, d, *J* 7, NCHCH_3), 1.30–1.10 [8H, m, $(CH_2)_4$], 1.0–0.8 [6H, d × 2, *J* 7, NCH$(CH_3)_2$], 0.80 (3H, t, *J* 7, CH_3); δ_C(75 MHz, $CDCl_3$) 169.4 (C=O), 155.8, 135.4, 134.7, 130.8, 128.5, 126.5, 125.6, 121.1, 120.8, 106.3 (ArC), 87.4 (COH), 80.8, 69.5 (alkyne), 61.5 (OMe), 50.9, 45.8 (NCH × 2), 31.2, 28.7, 28.3, 22.4, 20.4 (5 × CH_2), 20.1, 19.4, 18.8, 18.7 (4 × CH_3), 13.9 (CH_3); *m*/*z* (CI) 424 (100%, $(M + H)^+$), (EI) 86 (100, 2 × *i*-Pr), 43 (79, *i*-Pr) (Found (EI): M^+, 423.2770. $C_{27}H_{37}NO_3$ requires *M*, 423.2773).

Also obtained was the *syn alcohol syn*-**46b** (73 mg, 37%) as a pale yellow oil; R_f [1:2 EtOAc–petrol] 0.33; δ_H(300 MHz, $CDCl_3$) 8.00 (1H, d, *J* 8.5, ArH), 7.75 (1H, d, *J* 8.5, ArH), 7.39 (1H, d, *J* 8, ArH), 7.34 (1H, t, *J* 8, ArH), 6.80 (1H, d, *J* 7, ArH), 5.70 (1H, s, HOC*H*), 3.85 (3H, s, OMe), 3.65 (1H, m, OH), 3.52 [1H, septet, *J* 7, NCH$(CH_3)_2$], 3.40 [1H, septet, *J* 7, NCH$(CH_3)_2$], 2.25 (2H, td, *J* 7 and 2, alkyne CH_2), 1.60 (3H, d, *J* 7, NCHCH_3), 1.55 (3H, d, *J* 7, NCHCH_3), 1.35 [2H, m, C$H_2(CH_2)_3CH_3$], 1.30–1.10 [6H, m, $(CH_2)_3CH_3$], 0.90 (3H, d, *J* 7, NCHCH_3), 0.85 (3H, d, *J* 7, NCHCH_3), 0.80 (3H, t, *J* 7, CH_3); δ_C(75 MHz, $CDCl_3$) 169.4 (C=O), 155.8, 135.4, 134.7, 130.8, 128.5, 126.2, 125.6, 121.1, 120.8, 106.3 (ArC), 87.4 (COH), 80.8, 69.5 (alkyne), 61.5 (OMe), 50.6, 45.8 (NCH × 2), 31.2, 28.4, 28.3, 22.4, 20.4 (5 × CH_2), 20.1, 19.4, 18.8, 18.7 (4 × CH_3), 13.9 (CH_3); *m*/*z* (CI) 424 (8%, $(M + H)^+$), (EI) 86 (98, 2 × *i*-Pr) (Found (EI): M^+, 423.2770. $C_{27}H_{37}NO_3$ requires *M*, 423.2773).

Method C. Alternatively, *n*-butyllithium (1.1 ml of a 1.6 M solution in hexane) was added dropwise to a stirred solution of oct-1-yne (0.2 ml, 1.4 mmol) in THF (10 ml) under nitrogen at −78 °C. After 30 min at −78 °C DIBAL-H (1.4 ml, 1.4 mmol) was added and the mixture stirred at this temperature for 30 min. The aldehyde **42** (150 mg, 0.48 mmol) was added and the mixture was stirred for 30 min at −78 °C and warmed to room temperature. Saturated aqueous NH_4Cl was added and the mixture was extracted with dichloromethane (2 × 30 ml). The extracts were washed with brine (30 ml), dried ($MgSO_4$) and evaporated under reduced pressure. Analytical HPLC of the crude mixture showed that the atropisomers were present in a ratio of >99 (*anti*):1 (*syn*). Purification by column chromatography [1:2 EtOAc–petrol] gave only *anti*-**46b** (130 mg, 65%). On one occasion, using an essentially identical method, aldehyde **42** (2.0 g, 6.4 mmol) gave *N,N-diisopropyl-2-(hydroxymethyl)-8-methoxy-1-naphthamide* **51** (1.8 g, 88%) as a white solid; mp 205–207 °C; R_f [1:4 EtOAc–petrol] 0.45; δ_H(300 MHz, $CDCl_3$) 7.60 (1H, d, *J* 8.5, ArH), 7.43 (1H, d, *J* 8, ArH), 7.28 (1H, d, *J* 8.5, ArH), 7.24 (1H, t, *J* 8, ArH), 6.73 (1H, d, *J* 6, ArH), 4.76 (1H, d, *J* 12, C$H_A$$H_B$OH), 4.40 (1H, d, *J* 12, CH_A-H_BOH), 3.78 (3H, s, OMe), 3.44 [1H, septet, *J* 7, NCH$(CH_3)_2$], 3.28 [1H, septet, *J* 7, NCH$(CH_3)_2$], 1.60 (3H, d, *J* 7, NCHCH_3), 1.55 (3H, d, *J* 7, NCHCH_3), 0.85 (3H, d, *J* 7, NCHCH_3), 0.80 (3H, d, *J* 7, NCHCH_3); δ_C(75 MHz, $CDCl_3$) 171.8 (C=O), 135.2, 134.4, 128.5, 128.4, 127.8, 126.4, 126.2, 125.7, 120.8, 120.8 (ArC), 105.9 (CH_2OH), 62.7 (OMe), 50.8, 45.9 (NCH × 2), 20.4, 20.3, 20.2, 19.4 (4 × CH_3); *m*/*z* (CI) 316 (32%, $(M + H)^+$), 102 (100), (EI) 199 (27), 86 (55, 2 × *i*-Pr), 84 (70) and 49 (100) (Found (EI): M^+, 315.1838. $C_{19}H_{25}NO_3$ requires *M*, 315.1834).

Method D. Alternatively, *n*-butyllithium (1.1 ml; 1.6 M solution in hexane) was added dropwise to a stirred solution of oct-1-yne (0.2 ml, 1.4 mmol) in THF (10 ml) under nitrogen at −78 °C. After 30 min at −78 °C Me_3Al (24 μl; 2 M solution in hexane) was added and the mixture stirred at this temperature for 30 min. The *aldehyde* **42** (150 mg, 0.48 mmol) was added and the mixture stirred for 30 min at −78 °C and the mixture warmed to room temperature for 30 min. Saturated aqueous NH_4Cl was added and the product extracted with dichloromethane (2 × 30 ml). The extracts were washed with brine (30 ml), dried ($MgSO_4$) and evaporated under reduced pressure. Analytical HPLC of the crude mixture showed that the atropisomers were present in a ratio of 21 (*anti*):1 (*syn*). Purification by column chromatography on SiO_2 [1:2 EtOAc–petrol] gave *anti*-**46b** (81 mg, 40%).

When Et_3Al was used in place of Me_3Al, only starting material (97%) was recovered.

(*S*a,1′*R*)-*N*,*N*-Diisopropyl-2-(1′-hydroxynon-2′-ynyl)-8-methoxy-1-naphthamide (+)-*anti*-46b

By method D, enantiomerically pure (−)-**42** (0.37 g, 1.17 mmol) gave *optically active alcohol* (+)-*anti*-**46b** (0.20 g, 40%) as white plates; mp 122–126 °C; $[a]_D^{23}$ +61 (*c* = 1, CH_2Cl_2).

(*R*a,2′*R*,4′*S*)-*N*,*N*-Diisopropyl-8-(dimethylamino)-2-[2′-phenylperhydropyrrolo[1,2-*c*]imidazol-3′-yl]-1-naphthamide 53a

The diamine **52**[63] (75 mg, 0.46 mmol) was added to a solution of the aldehyde **41** (150 mg, 0.46 mmol) in toluene (20 ml). The solution was heated to reflux in a Dean–Stark apparatus for 20 h, cooled and the toluene was removed under reduced pressure. Purification by flash chromatography on alumina [1:20 EtOAc–petrol] gave the *aminal* **53a** (170 mg, 79%) as colourless plates; R_f [1:20 EtOAc–petrol] 0.40; ν_{max} (film)/cm^{-1} 2928 (CH), 1618 (N–C=O); δ_H(300 MHz, $CDCl_3$) 7.65 (1H, d, *J* 8, ArH), 7.40 (1H, d, *J* 7, ArH), 7.35 (1H, t, *J* 8, ArH), 7.20 (1H, d, *J* 8, ArH), 7.10 (1H, d, *J* 8, ArH), 7.10 (2H, 2 × t, *J* 7, ArH), 6.75 (2H, 2 × d, *J* 8, ArH), 6.60 (1H, t, *J* 7, ArH), 6.10 (1H, s, NCHN), 4.1 (1H, t, *J* 7, NC*H*CH_2), 3.95 (1H, t, *J* 7, PhNC$H_A$$H_B$), 3.44 (1H, septet, *J* 7, NC*H*CH_3), 3.3 (2H, m, NCH_2-CH_2 and C), 2.80 (3H, s, NMe), 2.75 (2H, m, NC*H*CH_3 and PhNC$H_A$$H_B$), 2.60 (3H, s, NMe), 2.00–1.80 (4H, m, CH_2CH_2), 1.65 [6H, 2 × d, *J* 7, NCH$(CH_3)_2$], 0.90 (3H, d, *J* 7, NCHCH_3), 0.7 (3H, d, *J* 7, NCHCH_3); *m*/*z* (CI) 485 (50%, $(M + H)^+$), (EI) 86 (63, 2 × *i*-Pr) (Found (EI): $(M + H)^+$, 485.3278. $C_{31}H_{40}N_4O$ requires *M* + 1, 485.3280).

(*S*a,2′*R*,4′*S*)-*N*,*N*-Diisopropyl-8-methoxy-2-[2′-phenylperhydropyrrolo[1,2-*c*]imidazol-3-yl]-1-naphthamide 54a

The diamine **52**[63] (470 mg, 2.9 mmol) was added to a solution of the aldehyde **42** (600 mg, 1.9 mmol) in xylene (50 ml). The solution was heated to reflux in a Dean–Stark apparatus for 3 days and cooled and the xylene was removed under reduced pressure. Purification of the crude product (obtained in quantitative yield) by column chromatography on alumina [1:4 EtOAc–petrol] gave the aminal **54a** (540 mg, 60%) as an amorphous solid; mp 207–210 °C; R_f [1:4 EtOAc–petrol] 0.23; ν_{max} (film)/cm^{-1} 2968 (CH), 1623 (N–C=O); δ_H(300 MHz, $CDCl_3$) 7.56 (1H, d, *J* 8.5, ArH), 7.27 (2H, 2 × d, *J* 7, ArH), 7.18 (1H, t, *J* 8.5, ArH), 7.06 (2H, t, *J* 7, ArH), 6.76 (1H, t, *J* 5, ArH), 6.62 (2H, d, *J* 8, ArH), 6.49 (1H, t, *J* 7, ArH), 5.92 (1H, s, NCHN), 4.08 (1H, m, NC*H*CH_2), 3.86 (3H, s, OMe), 3.74 (1H, t, *J* 8, PhNC$H_A$$H_B$), 3.52 (1H, septet, *J* 7, NC*H*$(CH_2)_2$), 3.30 [3H, m, NC*H*$(CH_3)_2$ and NCH_2CH_2], 2.62 (1H, q, *J* 7, PhNC$H_A$$H_B$), 2.00–1.80 (4H, m, CH_2CH_2), 1.70 [6H, 2 × d, *J* 7, NCH$(CH_3)_2$], 1.14 (3H, d, *J* 7, NCHCH_3), 0.84 (3H, d, *J* 7,

NCHCH_3); δ_C(75 MHz, $CDCl_3$) 170.3 (C=O), 155.8, 145.5, 137.0, 134.4, 131.9, 129.1, 128.2, 125.9, 124.7, 121.7, 120.8, 115.7, 112.2, 105.9 (ArC), 79.5 (Ar*C*HR_2), 60.6 (OMe), 55.3, 53.6, 52.7 (ring C), 50.9, 46.0 (NCH × 2), 27.9, 23.4 (ring C), 21.3, 20.4, 19.8, 19.7 (4 × CH_3); *m/z* (CI) 472 (100%, $(M + H)^+$), (EI) 471 (17, M), 427 (100), 212 (100) and 86 (52, 2 × *i*-Pr) (Found (EI): M^+, 471.2892. $C_{30}H_{37}N_3O_2$ requires *M*, 471.2886).

(*R*)-*N*,*N*-Diisopropyl-2-formyl-8-methoxy-1-naphthamide (−)-42

1 M aqueous HCl (50 ml) was added to a solution of the crude mixture of diastereoisomers of aminal **54** (0.124 g, 0.27 mmol) in methanol at 0 °C. After 30 min at room temperature the mixture was extracted with dichloromethane (2 × 60 ml). The extracts were washed with sodium bicarbonate solution and with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was recrystallised from ethyl acetate to give the aldehyde (−)-**42** (78 mg, 92%) as white prisms; mp 190–192 °C; $[a]_D^{23}$ −9.2 (*c* = 1, CH_2Cl_2). Analytical HPLC of the crude reaction mixture on chiral stationary phase indicated 62% ee.

In the same way, hydrolysis of purified **54a** (1.0 g, 2.12 mmol) gave a residue which was recrystallised from ethyl acetate to give the *aldehyde* (−)-**42** (627 mg, 94%) as white prisms; mp 191–192 °C, $[a]_D^{23}$ −15 (*c* = 1, CH_2Cl_2). Analytical HPLC of the crude reaction mixture on chiral stationary phase indicated 99% ee. Evaporation of the mother liquors returned diamine **52** (270 mg, 80%).

(S_a,1′*S*)-*N*,*N*-Diisopropyl-2-[(2*E*)-1′-hydroxynon-2-enyl]-8-methoxy-1-naphthamide (*E*)-57

Red-Al® (0.17 ml, 0.87 mmol) was added dropwise over 20 min to the alkyne (+)-*anti*-**46b** (184 mg, 0.43 mmol) in ether (5 ml) at 0 °C under nitrogen. After 1 h, water (2 ml) was added dropwise and the mixture, which was extracted into ether. The extracts were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. Purification by column chromatography on SiO_2 [1:4 EtOAc–petrol] gave the *alkene* (*E*)-**57** (183 mg, 99%) as a yellow oil; R_f [1:4 EtOAc–petrol] 0.26; $[a]_D^{23}$ +130 (*c* = 1, EtOH); ν_{max} (film)/cm^{-1} 3424 (OH), 2926 (CH), 1616 (C=O), 828 (alkene CH); δ_H(300 MHz, $CDCl_3$) 7.72 (1H, d, *J* 8.5, ArH), 7.56 (1H, d, *J* 8.5, ArH), 7.34 (2H, m, ArH), 6.80 (1H, dd, *J* 7, ArH), 5.70 (2H, m, CH=CH), 5.43 [1H, fine m, C*H*OH], 3.84 (3H, s, OMe), 3.50 [2H, septet × 2, *J* 7, NC*H*$(CH_3)_2$], 1.90 [2H, m, C$H_2(CH_2)_4CH_3$], 1.60 (3H, d, *J* 7, NCHCH_3), 1.55 (3H, d, *J* 7, NCHCH_3), 1.20 [8H, m, $(CH_2)_4$-CH_3], 0.90 (3H, d, *J* 7, NCHCH_3), 0.85 (3H, d, *J* 7, NCHCH_3), 0.80 (3H, t, *J* 7, CH_3); δ_C(75 MHz, $CDCl_3$) 169.7 (C=O), 155.8, 136.8 (alkene), 134.5, 132.2, 131.2, 130.5, 128.5, 126.2, 124.7, 121.2, 120.8, 106.2 (ArC), 71.1 (R*C*H(OH)R), 55.2 (OMe), 50.6, 45.7 (CHN × 2), 32.1, 31.6, 28.9, 28.8, 22.5 (5 × CH_2), 20.5, 20.4, 20.3, 19.5 (4 × CH_3), 13.9 (CH_3); *m/z* (CI) 426 (18%, $(M + H)^+$), 408 (80), 102 (100), (EI) 408 (50), 324 (52) and 86 (100, 2 × *i*-Pr) (Found (EI): M^+, 425.2926. $C_{27}H_{39}NO_3$ requires *M*, 425.2929).

(S_a,1′*S*) *N*,*N*-Diisopropyl-2-[(2*Z*)-1′-hydroxynon-2′-enyl]-8-methoxy-1-naphthamide (*Z*)-57

Alkyne (+)-*anti*-**46b** (209 mg, 0.5 mmol) and Lindlar catalyst (42 mg, cat.) were stirred in *n*-BuOH (50 ml) at room temperature under 1 atm of hydrogen. After hydrogen uptake ceased in 24 h, the mixture was filtered through a thin pad of Celite, washed with EtOAc, dried ($MgSO_4$) and the solvent removed under reduced pressure. Purification by column chromatography [1:4 EtOAc–petrol] gave the *alkene* (*Z*)-**57** (180 mg, 85%) as a yellow oil; R_f [1:4 EtOAc–petrol] 0.44; $[a]_D^{23}$ +130 (*c* = 1, EtOH); ν_{max} (film)/cm^{-1} 3424 (OH), 2928 (CH), 1617 (C=O); δ_H(300 MHz, $CDCl_3$) 7.84 (1H, d, *J* 8.5, ArH), 7.72 (1H, d, *J* 8.5, ArH), 7.40 (2H, m, ArH), 6.90 (1H, dd, *J* 6.5, ArH), 5.76 (2H, m, RC*H*OH and alkene), 5.55 (1H, dd, *J* 9 and 7, *cis* alkene), 3.94 (3H, s, OMe), 3.64 [1H, septet, *J* 7, NC*H*$(CH_3)_2$], 3.48 [1H, septet, *J* 7, NC*H*$(CH_3)_2$], 2.30 [2H, m, $CH_2(CH_2)_4$-CH_3], 1.80 (3H, d, *J* 7, NCHCH_3), 1.75 (3H, d, *J* 7, NCHCH_3), 1.50–1.10 [8H, m, $(CH_2)_4CH_3$], 1.00 (3H, d, *J* 7, NCHCH_3), 0.95 (3H, d, *J* 7, NCHCH_3), 0.80 (3H, t, *J* 7, CH_3); δ_C(75 MHz, $CDCl_3$) 169.8 (C=O), 155.8 (alkene), 137.4, 133.3, 131.3, 130.5, 128.5, 126.2, 125.2, 121.2, 120.7, 106.2 (ArC), 66.6 (HCOH), 55.2 (OMe), 50.6, 45.8 (NCH × 2), 31.6, 29.4, 28.9, 27.6, 22.5, 21.0 (CH_2 × 6), 20.3, 20.2, 20.1, 19.4 (4 × CH_3), 14.0 (CH_3); *m/z* (CI) 426 (5%, $(M + H)^+$), 102 (100), (EI) 391 (52), 167 (65), 86 (42, 2 × *i*-Pr) and 74 (100) (Found (EI): M^+, 425.2921. $C_{27}H_{39}NO_3$ requires *M*, 425.2929).

(3′*R*)-*N*,*N*-Diisopropyl-2-[(*E*)-3′-(*N*,*N*-dimethylcarbamoylmethyl)non-1′-enyl]-8-methoxy-1-naphthamide 59

N,*N*-Dimethylacetamide dimethyl acetal (100 µl, 0.75 mmol) was added to a solution of the *cis* alcohol (*Z*)-**57** (64 mg, 0.15 mmol) in xylene (20 ml). The solution was heated to reflux for 20 h, cooled, and poured into dichloromethane (25 ml) and saturated aqueous NH_4Cl (25 ml). The layers were separated, and the aqueous layer extracted with dichloromethane (2 × 25 ml). The combined organic fractions were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by column chromatography [1:1 EtOAc–petrol] gave one diastereoisomer of the *amide* **59** as a pale yellow oil (20 mg, 27%); R_f (EtOAc) 0.40; $[a]_D^{23}$ +27.6 (*c* = 1, EtOH); ν_{max} (film)/cm^{-1} 2928 (CH), 1630 (C=O); δ_H(300 MHz, $CDCl_3$) 7.70 (2H, s, ArH), 7.35 (2H, m, ArH), 6.85 (1H, d, *J* 7, ArH), 6.80 (1H, d, *J* 15.5, *trans* alkene), 6.40 (1H, dd, *J* 8 and 15.5, *trans* alkene), 3.95 (3H, s, OMe), 3.50 [2H, 2 × septet, *J* 7, NC*H*$(CH_3)_2$], 3.05 (3H, s, NMe), 2.95 (3H, s, NMe), 2.80 (1H, m, alkene-C*H*R_2), 2.45 (2H, 2 × d, *J* 7, NCHCH_3), 1.70 (3H, d, *J* 7, NCHCH_3), 1.65 (3H, d, *J* 7, NCHCH_3), 1.30 (3H, d, *J* 7, NCHCH_3), 1.40–1.20 [10H, m, $(CH_2)_5CH_3$], 0.95 (3H, d, *J* 7, NCHCH_3), 0.85 (3H, t, *J* 7, CH_3); δ_C(75 MHz, $CDCl_3$) 171.7, 170.3, 155.7, 135.7, 134.2, 131.2, 130.9, 127.8, 126.8, 125.9, 123.7, 121.7, 120.8, 106.2, 55.2, 50.9, 45.7, 39.4, 38.7, 37.4, 35.4, 35.0, 31.7, 22.6, 20.5, 20.4, 20.3, 14.1 (Found (EI): M^+, 494.3511. $C_{31}H_{46}N_2O_3$ requires *M*, 494.3508).

Also obtained was a second diastereoisomer of *amide* **59** as a pale yellow oil (10 mg, 14%); R_f (EtOAc) 0.15; ν_{max} (film)/cm^{-1} 2894 (CH), 1641 (C=O); δ_H(300 MHz, $CDCl_3$) 7.70 (2H, m, ArH), 7.35 (2H, m, ArH), 6.85 (1H, d, *J* 7, ArH), 6.80 (1H, d, *J* 15.5, *trans* alkene), 6.25 (1H, dd, *J* 8, 15.5, *trans* alkene), 3.90 (3H, s, OMe), 3.50 [2H, 2 × septet, *J* 7, NC*H*$(CH_3)_2$], 3.00 (3H, s, NMe), 2.95 (3H, s, NMe), 2.75 (1H, m, alkene-C*H*R_2), 2.45 (2H, 2 × d, *J* 7, NCH$(CH_3)_2$), 1.70 (3H, d, *J* 7, NCHCH_3), 1.65 (3H, d, *J* 7, NCHCH_3), 1.40–1.10 [10H, m, $(CH_2)_5CH_3$], 0.95 (3H, d, *J* 7, NCHCH_3), 0.90 (3H, d, *J* 7, NCHCH_3), 0.85 (3H, t, *J* 7, CH_3); δ_C(75 MHz, $CDCl_3$) 171.6, 170.3, 155.7, 135.6, 134.2, 131.0, 131.0, 127.8, 127.0, 125.9, 123.5, 121.6, 120.8, 55.2, 50.9, 45.8, 39.2, 37.5, 35.4, 34.9, 31.8, 29.3, 27.7, 22.6, 20.8, 20.5, 14.0 (Found (EI): M^+, 494.3513. $C_{31}H_{46}N_2O_3$ requires *M*, 494.3508).

Ethyl (S_a,1*R*,*E*)-5-[1-(diisopropylcarbamoyl)-8-methoxy-2-naphthyl]-3-hexylpent-4-enoate 64

Triethyl orthoacetate (26 µl, 0.14 mmol) and propionic acid (1 µl, cat.) were added to a solution of the *alcohol* (*Z*)-**57** (20 mg, 0.05 mmol) in toluene (20 ml). The solution was heated to reflux for 12 h, cooled, and concentrated under reduced pressure. Purification by flash chromatography [1:4 EtOAc–petrol] gave a single diastereoisomer of the *ester* **64** as a pale yellow oil (21 mg, 84%); R_f [1:4 EtOAc–petrol] 0.38; $[a]_D^{23}$ +20 (*c* = 1, EtOH); δ_H(300 MHz, $CDCl_3$) 7.62 (2H, s, ArH), 7.28 (2H, m, ArH), 6.78 (1H, d, *J* 7, ArH), 6.73 (1H, d, *J* 16, *trans* alkene), 6.08 (1H, dd, *J* 8 and 16, *trans* alkene), 4.05 (2H, m, OCH_2CH_3), 3.83 (3H, s, OMe), 3.40 [2H, 2 × septet, *J* 7,

N(C*H*(CH_3)$_2$)$_2$], 2.65 (1H, m, CH_2=CH_2C*H*R_2), 2.38 (2H, 2 × d, *J* 7, EtOCOC*H*$_2$$R_2$), 1.60 (3H, d, *J* 7, NCHC*H*$_3$), 1.55 (3H, d, *J* 7, NCHC*H*$_3$), 1.40 [2H, m, C*H*$_2$(CH_2)$_4$$CH_3$], 1.30–1.10 [14H, m, NCHC*H*$_3$, (CH_2)$_4$$CH_3$ and OCH_2C*H*$_3$], 0.90 (3H, d, *J* 7, NCHC*H*$_3$), 0.80 [3H, t, *J* 7, (CH_2)$_5$C*H*$_3$]; δ_C(75 MHz, $CDCl_3$) 172.4, 170.2, 155.7, 134.8, 134.3, 131.2, 131.1, 128.4, 127.7, 127.6, 125.9, 123.7, 120.8, 106.2, 60.1, 55.3, 50.9, 45.8, 40.1, 39.4, 34.9, 31.6, 29.8, 26.9, 22.6, 20.4, 20.3, 19.6, 14.2, 14.0. (Found (EI): M^+, 495.3343. $C_{31}H_{45}NO_4$ requires *M*, 495.3348).

(*R*)-3-(Hydroxymethyl)-*N*,*N*-dimethylnonamide (−)-61[15]

A solution of naphthamide **59** (30 mg, 0.06 mmol) in MeOH at 0 °C was treated with a steady stream of ozone in oxygen for 60 min at 0 °C. Excess ozone was removed by passing a stream of oxygen through the reaction mixture for 10 min, and the reaction mixture was diluted with 50% aqueous ethanol (8 ml). Sodium borohydride (23 mg, 0.6 mmol) was carefully added, and the reaction mixture was allowed to warm to 23 °C and stirred for a further 1 h. Concentrated hydrochloric acid (0.5 ml) and EtOAc (30 ml) were added. The solution was washed with saturated aqueous $NaHCO_3$ (10 ml), water (10 ml) and brine (10 ml), dried (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography (1 : 1 MeOH–EtOAc) gave the *alcohol* (−)-**61**[15] as a pale yellow oil (10 mg, 77%); R_f [1 : 1 EtOAc–petrol] 0.25; δ_H(300 MHz, $CDCl_3$) 3.70 (1H, dd, *J* 11 and 4, C*H*$_A$$H_B$OH), 3.50 (1H, dd, *J* 11 and 4, CH_A*H*$_B$OH), 3.08 (3H, s, N*Me*$_A$$Me_B$), 3.00 (3H, s, N$Me_A$*Me*$_B$), 2.53 (1H, dd, *J* 4 and 16, OCC*H*$_A$$H_B$), 2.40 (1H, dd, *J* 9 and 16, OCH_A*H*$_B$), 2.10 (1H, m, HOCH_2C*H*), 1.30 [10H, m, (CH_2)$_5$], 0.9 (3H, t, *J* 7, CH_2*Me*).

Also obtained was *2-(N,N-diisopropylcarbamoyl)-3,6-bis-(hydroxymethyl)benzoic acid* **60**; δ_H(300 MHz, $CDCl_3$) 7.73 (1H, d, *J* 8, ArH), 7.40 (1H, d, *J* 8, ArH), 5.25 (2H, m, ArC*H*$_2$OH), 4.73 (1H, dd, *J* 12.5 and 1.5, ArC*H*$_A$$H_B$OH), 4.46 (1H, dd, *J* 12.5 and 9, ArCH_A*H*$_B$OH), 3.6–3.4 (2H, m, NCH × 2), 1.61 (3H, d, *J* 7, Me), 1.54 (3H, d, *J* 7, Me), 1.12 (3H, d, *J* 7, Me), 1.00 (3H, d, *J* 7, Me); *m*/*z* (CI) 292 (100%, $(M - OH)^+$).

Determination of enantiomeric excess of (−)-61. (+)-MTPACl (17 mg, 0.069 mmol) was added to a solution of alcohol (−)-**61** (10 mg, 0.046 mmol), Et_3N (19 μl, 0.138 mmol), and DMAP (3 mg) in $CDCl_3$ (100 μl). After 1 h, ^{1}H NMR of the mixture revealed complete consumption of **61** and conversion into a single diastereoisomer of **62**. Comparison with the diastereoisomeric esters formed from (+)- or (±)-MTPACl and (+)-**61**[15] showed that the ee of (−)-**61** was >90%.

X-Ray crystallography

Crystal data for *syn*-**46b**: $C_{27}H_{37}NO_3$, M_r = 423.58. A colourless block (*ca*. 0.50 × 0.37 × 0.35 mm^3) was mounted on a glass fibre and analysed with a Rigaku AFC-5R diffractometer. Cu-Kα radiation (λ = 1.5418 Å), triclinic, space group $P\bar{1}$, *a* = 11.0048(15), *b* = 12.0970(18), *c* = 10.7206(16) Å, α = 103.229(13), β = 94.072(14), γ = 113.705(11)°, *V* = 1250.6(3) Å^3, *Z* = 2, ρ_{calcd} = 1.125 Mg m^{-3}, μ(Cu-Kα) = 0.566 mm^{-1}. Total number of reflections measured = 5244 of which 4966 were independent; R_{int} = 0.0154, 2850 reflections were observed, ($I > 2.0\sigma(I)$). Hydrogen atoms were included in constrained positions, except for H2, which was found by difference Fourier techniques and refined isotropically. Atoms of the C_6H_{13} group showed high thermal motion, especially towards the end of the chain. Refinement on F^2 with 290 parameters gave R_1 = 0.0728, wR^2 = 0.2382 (all data), *S* = 1.048, Δ/σ_{max} = 0.003. Maximum and minimum residual electron density = 0.271 and −0.217 e Å^{-3} respectively. Data collection: MSC/AFC Diffractometer Control. Cell refinement: MSC/AFC Diffractometer Control. Data reduction: teXsan.[74] Program used to solve structure: SHELXS86. Program used to refine structure: SHELXL97.[75]

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