Atropisomeric amides: stereoselective enolate chemistry and enantioselective synthesis *via* a new SmI_2-mediated reduction

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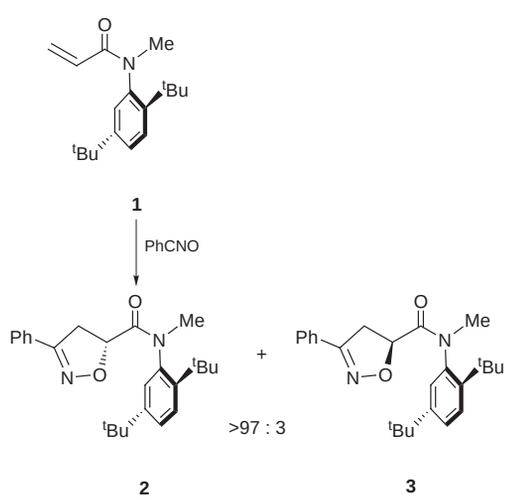
The use of certain types of atropisomeric amides, incorporating an *N*-MEM-*ortho*-*tert*-butylaniline group, for stereoselective reactions, has been explored. Enolate reactions of these systems are highly diastereocontrolled, and enantiomerically enriched starting materials can be obtained, starting from lactic acid, *via* a new SmI_2 mediated reduction process.

Introduction

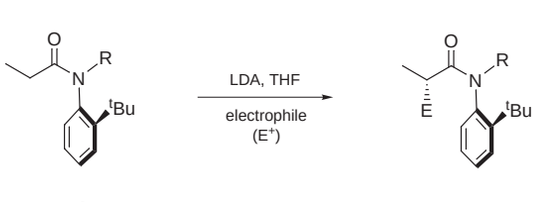
In 1994 a report from Curran's group described the powerful stereodirecting potential of certain types of axially twisted amides.[1] For example, atropisomeric amide **1** was shown to undergo a cycloaddition reaction with a nitrile oxide to give product **2**, rather than **3**, with excellent levels of diastereocontrol, Scheme 1. In such reactions the formation of products



Scheme 1

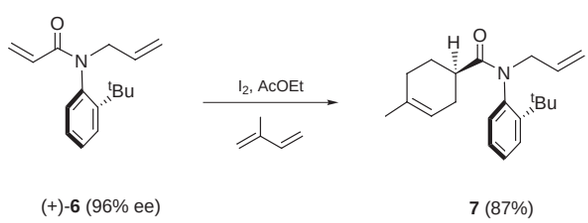
having stereogenic centres is controlled by the chiral aryl-C–N axis in the starting material. Radical reactions with these amide systems, and also with related cyclic imides, were also found to proceed with good selectivity.

Our own interest in this area lay in the possibility of using this type of stereocontrol in reactions of enolates, for example the diastereocontrolled alkylation of **4** to give **5**, Scheme 2. This type of reaction posed special problems, which we were able to solve only by careful choice of the additional nitrogen substituent R, as described in our initial communication in this area, *vide infra*.[2]



Scheme 2

In addition to the question of diastereocontrol in this type of reaction is the issue of availability of the starting atropisomeric amides in enantiomerically enriched form. Although we managed to acquire small amounts of enantiomerically enriched atropisomeric amide by means of a rather inefficient kinetic resolution procedure, it was Taguchi and co-workers who first described an effective access to these compounds *via* a chiral pool approach.[3,4] For example, they were able to prepare (+)-**6** in 96% ee, starting from (*S*)-*O*-acetyllactic acid, and also demonstrated further highly stereocontrolled chemistry of these compounds, such as an iodine-activated Diels–Alder cycloaddition to generate **7**, Scheme 3.

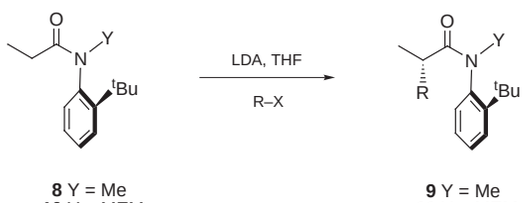


Scheme 3

Our contemporaneous studies of the chiral pool approach to these atropisomeric amides followed a similar strategy, and unearthed a new samarium-mediated reduction reaction.[5] In this paper we provide full details of this work, along with the previous studies of enolate alkylation and aldol reaction.

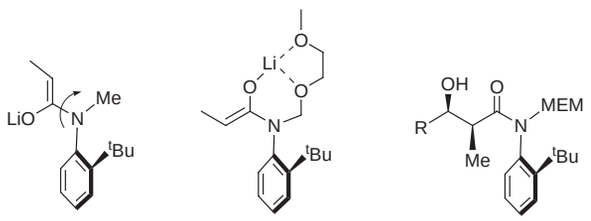
Enolate chemistry with racemic atropisomeric amides

Our initial experiments involved alkylation reactions of the lithium enolate derived from anilide **8** by treatment with LDA. These reactions gave the desired products **9** in good chemical yield but with very modest diastereoselectivities of around 2–4 : 1 (Scheme 4). Since with a bulky amide such as

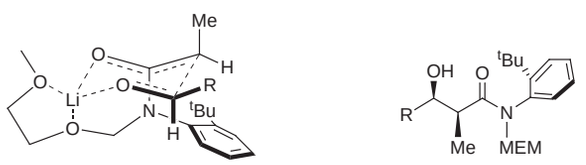


Scheme 4

8 the (*Z*)-enolate should be efficiently formed, we attributed this poor level of selectivity to the possibility of rotation around the amide C–N bond in the intermediate enolate, as illustrated by **12**. An obvious approach to controlling the



12 **13** **14**



15 **16**

conformation of such enolates would be to introduce a metal co-ordinating group Y into the *N*-substituent. Initial attempts, using imide type derivatives with Y = Boc or CO^{t}Bu were unrewarding, these compounds not forming enolates, but in the latter case acting as an acylating agent. We turned instead to the *N*-MEM derivative **10**, which we hoped might fix the conformation of the enolate by co-ordination, as shown in **13**.

Pleasingly, the enolate reactions of **10**, with simple electrophiles, such as alkyl halides, proved much more stereoselective than those involving **8**, Table 1.

In each case we assumed that the major product was **11**, corresponding to reaction on the face of the enolate not shielded by the *ortho-tert*-butyl group, which is consistent with all of the literature chemistry, and with our later findings, *vide infra*. NMR spectra of the crude products were very clean, and in each case we were able to identify the minor diastereoisomer by thermal atropisomerisation. For example, elevated temperature NMR studies showed that the isomer ratio of **11** (R = Bn) changed from 25:1 to only 2:1 after warming to 95 °C for 65 minutes.

We also examined the aldol reactions of **10**, involving addition of achiral aldehydes to the lithium enolate in THF, Table 2.

With a range of bulky or branched chain aldehydes, and even with propanal, the aldol products **14** were obtained with very good diastereoselectivity. The lability of the MEM group in the starting amide **10** precluded the use of alternative aldol strategies, involving the use of $TiCl_4$ or Bu_2BOTf.[6] We anticipated that the major aldol product would be the *syn*-isomer **14** resulting from reaction of a (*Z*)-lithium enolate, *via* a transition state such as **15**, in which the bulky *ortho-tert*-butyl group in the enolate is orientated away from the approaching aldehyde. This expectation was confirmed following a single crystal X-ray structure determination for the product **14** (R = Ph) from reaction with benzaldehyde, as revealed in our initial communication.[2]

A problem with determining the degree of stereoselectivity in these aldol reactions was the presence of additional conformers, compared to simple alkylations. Although we could reasonably assign the atropselectivities indicated (*i.e.* with respect to the anilide *aryl* C–N axis), the NMR spectra of the aldol products also showed additional minor signals attributed to *amide* C–N rotamers (*E*/*Z* rotamers), *e.g.* **16**. This problem has been discussed by Curran in a recent full paper in which he explores the conformational aspects of a wide range of anilides, and in which he coins the term "prochiral auxiliary" to describe this approach to asymmetric synthesis.[7] In our case, the presence of minor (*Z*)-conformers in the products was a

Table 1 Yields and diastereoselectivities in enolate reactions of amide **10**

Electrophile	Yield **11** (%)	Diastereomer ratio
$PhCH_2Br$	83	25:1
$H_2C{=}CHCH_2Br$	82	15:1
EtI	89	15:1
$PhCH{=}CHCH_2Cl$	69	>25:1 [a]
$PhSSO_2Ph$	84	>25:1 [a]

[a] Only one diastereomer observed by NMR spectroscopy.

Table 2 Yields and diastereoselectivities in aldol reactions of amide **10**

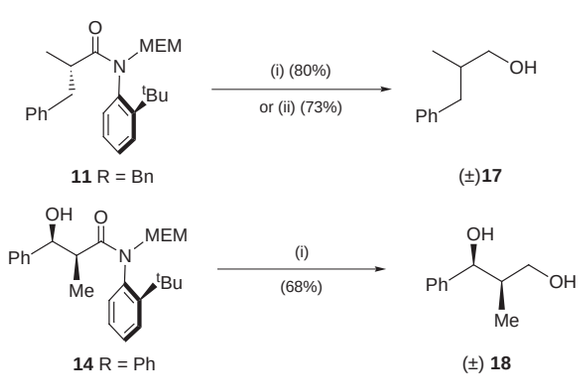
Aldehyde	Yield **14** (%)[a]
PhCHO	87
Me_2CHCHO	85
$C_6H_{11}CHO$	89
Me_3CCHO	87
EtCHO	86

[a] The *syn*-aldol product only was observed, all atropselectivities >25:1.

nuisance since it interfered with NMR analysis of the product ratios. Although we were reasonably confident that we could identify minor conformers by running NMR spectra in different solvents, we double-checked the initial selectivity figures by HPLC and found good agreement (*i.e.* there was at least a 25:1 ratio of isomers in every case).

Having demonstrated useful levels of diastereocontrol in preliminary enolate reactions of atropisomeric amides, the next immediate problem related to the release of chiral products from the anilide. A major disadvantage of these systems is the reluctance of the sterically hindered anilide to undergo hydrolysis to the corresponding carboxylic acid. Despite extensive efforts, involving the screening of many types of conditions we were unable to achieve this type of conversion. Curran has also commented upon this deficiency, and has examined alternative derivatives in which one of the methyls of the *tert*-butyl group is replaced by a trialkylsilyloxy group. Unfortunately, although these compounds show improved hydrolytic behaviour, the *aryl* C–N rotational barrier is somewhat reduced, leading to easier racemisation, and the compounds also seem to react with a lower degree of selectivity.

Instead, we demonstrated that release of chiral compounds is possible by reductive means, for example conversion of **11** into **17**, using either $LiAlH_4$ or LAB (lithium amidotrihydroborate),[8] and conversion of the aldol product **14** (R = Ph) into diol **18**, Scheme 5.



11 R = Bn (±)**17**

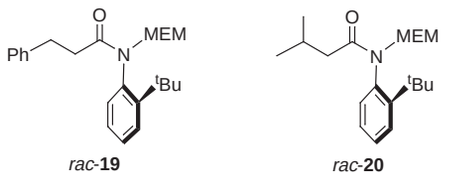
14 R = Ph (±) **18**

Scheme 5 *Reagents and conditions*: (i) $LiAlH_4$, THF, room temp.; (ii) LAB, THF, room temp.

In the first case we have repeated the cleavage with enantiomerically enriched material (*vide infra*) and demonstrated little or no loss in enantiomeric purity. In the case of **18** our observation of a single stereoisomer again indicates that

product epimerisation is not a problem. If desired it should be possible to oxidise such compounds to give the corresponding aldehydes or carboxylic acid derivatives.

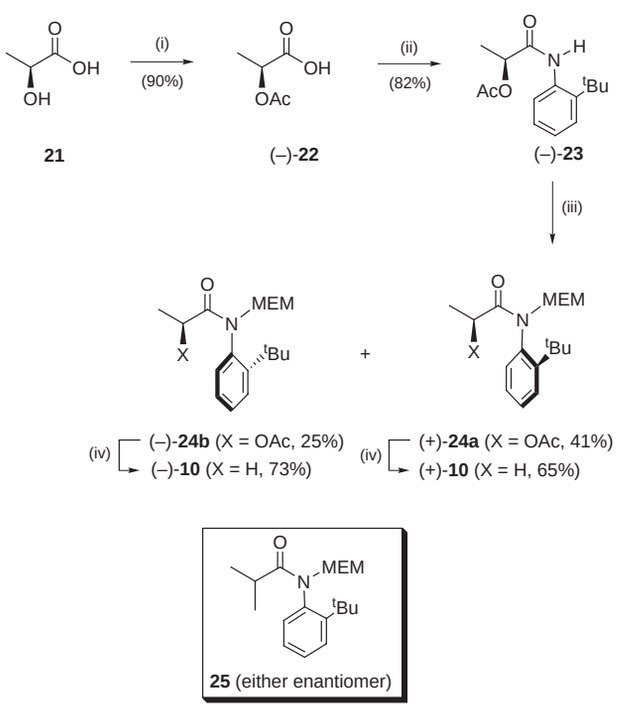
A final area of exploration involved examining the corresponding reactions of homologues of **10**, namely the phenethyl derivative **19** and the isobutyl variant **20**. Unfortunately the



enolate chemistry of these compounds was more complicated than for **10**, with **19** proving difficult to alkylate cleanly (giving starting material–product mixtures) and the *E*/*Z* rotamer complications discussed above being far more evident for products from **20**. At this point we chose to concentrate activity in the complementary area of work aimed at the synthesis of non-racemic anilides.

A chiral pool approach to non-racemic atropisomeric anilides

Although there are several conceivable approaches to our atropisomeric anilides in non-racemic form, including asymmetric synthesis and biocatalysis methods, we chose to concentrate on a method which would supply both enantiomers in highly enantiomerically enriched form. The route adopted is shown in Scheme 6, and involves manipulation of commercially

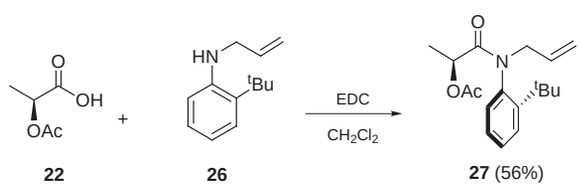


Scheme 6 *Reagents and conditions*: (i) AcCl, AcOH; (ii) EDC·HCl, CH_2Cl_2; (iii) NaH, THF, 0 °C then MEMCl; (iv) SmI_2 (4 equiv.), LiCl (12 equiv.), THF, room temp.

available L-(+)-lactic acid **21** (*ca.* 98% ee) in what amounts to a resolution procedure.

Acetylation of **21** gave the *O*-acetyl derivative **22**, which was then coupled with 2-*tert*-butylaniline using established peptide coupling techniques.[9] We found the yields of anilide **23** to be modest using many methods, the use of 3-ethyl-1-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDC·HCl) giving the best results (in related work the pyBOP reagent also gave good results). Anilide **23** was then *N*-alkylated with MEMCl in order to install the required MEM group, which furnished the two separable atropisomeric products **24a** and **24b**. At this point it was not possible to assign the relative stereochemistry of the aryl-C–N axis, which was deduced following subsequent transformations.

At this point we required a deoxygenation reaction in order to convert each of the diastereomeric amides **24** into the corresponding enantiomeric products **10**. It was anticipated that a direct deoxygenation should be possible using SmI_2, which has been used extensively in such reactions, but mainly involving α-heteroketones.[10] A search of the literature revealed a dearth of such amide reductions and established that SmI_2 had not been previously applied to amide deoxygenation.[11] Initial reactions of amides **24** with SmI_2 under standard conditions were somewhat sluggish, and only by adopting the recently reported protocol, involving addition of LiCl to the reaction mixture, were acceptable yields obtained.[12] This new reaction, the scope of which is outlined in more detail below, allowed us to isolate the required enantiomeric atropisomers **10** in good yield. The enantiomeric excess of these compounds proved difficult to determine, but was established to be ⩾93% following conversion to the corresponding α-methylated compounds **25**. The absolute configurations shown were deduced following further transformations, *vide infra*. At this point it is appropriate to compare our route with that of the Taguchi group, who also used this type of approach to access anilides such as **6**. Their sequence involved combining **22** with **26**, furnishing directly the mixture of atropisomers, of which **27** was the major isomer, Scheme 7.



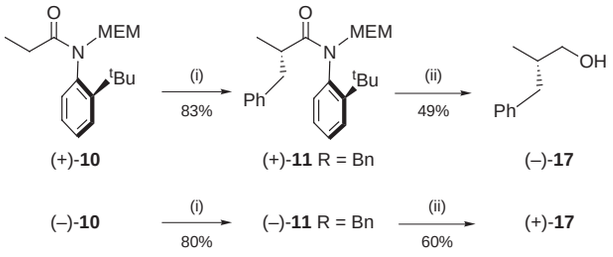
Scheme 7

It can be seen that this result differs somewhat from our experience in that **27** corresponds to **24b**, which we obtained as the *minor* isomer. That such differences in ratios are observed is not in the least surprising, given the different nitrogen substituents present, and also the different types of reaction in which the chiral C–N axis is established (amide coupling in the case of **26**, amide *N*-alkylation for **24**). We were denied the possibility of accessing amides **24** by an amide coupling analogous to that shown in Scheme 7 by the instability of the required *N*-MEM aniline. Conversion of **27** into **6** required acetate hydrolysis, alcohol activation by formation of the mesylate, selenide displacement and selenoxide *syn*-elimination.

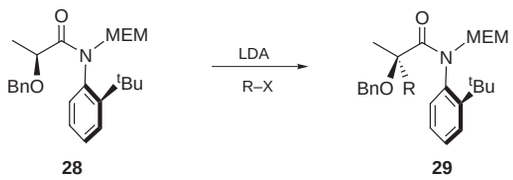
With highly enantiomerically enriched atropisomeric amides **10** in hand, we were able to repeat some of the chemistry illustrated earlier in Scheme 5 to access non-racemic products. In particular, we took each of the enantiomers (+)- and (−)-**10** and carried out benzylation followed by reductive removal of the auxiliary to give the primary alcohols (−)- and (+)-**17** respectively, as shown in Scheme 8.

Since the absolute configurations of these alcohol products are well established in the literature,[13] we were able to assign the configuration of the asymmetric carbon centre in the precursor amides **11**, and hence infer the configuration of the aryl C–N axis to be as shown in **10**, **11** and **24**. Comparison of optical rotation data also indicated that the optical purity of these compounds (*ca.* 93%) correlated well with the established enantiomeric excess of the precursor amides **10**.

One additional aspect of this chemistry which was briefly explored is illustrated in Scheme 9. By a sequence analogous to that shown in Scheme 6 for the *O*-acetyl series, we were also able



Scheme 8 *Reagents and conditions*: (i) LDA, THF, $PhCH_2Br$; (ii) $LiAlH_4$, THF.



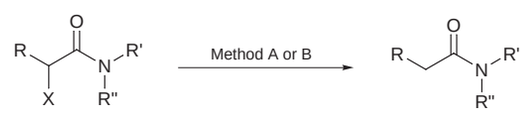
Scheme 9

to prepare the corresponding *O*-benzyl compounds, including **28** (as a separate atropisomer). It appeared possible that this compound could be alkylated stereoselectively *via* the corresponding enolate, which would give rise to amide derivatives of general structure **29**. This process would amount to a novel version of the "self-replication of chirality" principle, developed extensively by Seebach and co-workers,[14] and would allow the preparation of chiral α-alkoxy carboxylic acids and related products. Unfortunately, under a variety of conditions, we were unable to effect efficient enolate formation and alkylation. This problem is no doubt related to the difficulty we experienced in hydrolysing substituted amides **11**, and is due to the highly hindered nature of such systems.

A new SmI_2-mediated reduction of α-functionalised amides

Since the type of amide deoxygenation described above appeared rather rare, and the application of SmI_2 to such amide reduction was unprecedented,[15] we applied the new method to a range of other amides, according to Scheme 10, as shown in Table 3.

The reductions have not been fully optimised, and it is clear from the extended reaction time of at least 24 hours that is required that this is not a particularly facile process. Nevertheless, the reaction seems fairly general for different types of tertiary amide, and effects the removal of α-bromo, α-acetoxy and α-benzyloxy functions. In general we found it necessary to add LiCl to the reactions (Method A), although entries 4–6 show that debromination is rather more facile, and works well enough with SmI_2 alone (Method B). Debromination of a secondary amide is facile (entry 6), but other secondary amides gave either very poor yields of product (entry 9) or no reduction at all (entry 10). In the latter case only the hydroxy amide resulting from acetate cleavage was obtained (52%).



A - SmI_2 (4 equiv.), LiCl (12 equiv.), THF
B - SmI_2 (4 equiv.), THF

Scheme 10

Conclusions

Although several groups have now established the credibility of a chiral C–N axis as a stereocontrolling element for asymmetric synthesis a number of problems with this approach remain to be solved. Foremost amongst these is the need to establish more direct and efficient entries to the chiral amides (and imides, *etc.*) in enantiomerically pure form; clearly the chiral pool approach described above is not ideal. Other considerations include the development of alternative motifs for the chiral axis, which will allow easier manipulation of chiral products. If these types of difficulty can be overcome then the application of the "prochiral auxiliary" method to a wider range of reactions may become an attractive area for future exploration.

Experimental

General procedures

Melting points were determined on a Reichert Hot Stage apparatus and are uncorrected. Infrared spectra were recorded using a Perkin-Elmer 1600 series FTIR spectrophotometer as either sample solutions in chloroform or films. High resolution mass spectra were acquired on a VG Micromass 70E or AEI MS-902 mass spectrometer using electron impact (EI), chemical ionization (CI) or fast atom bombardment (FAB) using *meta*-nitrobenzyl alcohol (NBA) as the matrix. Microanalytical data were obtained on a Perkin-Elmer 240B elemental analyser. Optical rotations were recorded using a JASCO DIP-370 digital polarimeter. Proton NMR spectra were recorded on a Bruker WM 250 (250 MHz), a Bruker AM 400 (400 MHz), a Bruker DRX 500 (500 MHz) or a JEOL EX-270 (270 MHz) spectrometer either at ambient temperature or 333 K. The chemical shifts were recorded relative to an internal tetramethylsilane standard. All coupling constants, *J*, are reported in Hertz and abbreviations used are s - singlet, d - doublet, t - triplet, q - quartet, m - multiplet, dd - double doublet *etc.*, also br s - broad singlet, br d - broad doublet *etc.* The ratio of isomer mixtures were determined using ^1H NMR spectroscopy. Carbon-13 NMR spectra were either recorded on a JEOL EX 270 (68 MHz) spectrometer or a Bruker AM 400 (100 MHz) at ambient temperature. The multiplicities indicated were obtained using a DEPT sequence. Proton and carbon assign-

Table 3 SmI_2 Reduction of amides

Entry	R	R′	R″[a]	X	Method[b]	Product	Yield (%)
1	Me	Me	Ph	OAc	A	30	85
2	Me	MEM	Ar	OBn	A	10	69
3	Me	Me	Ar	OBn	A	31	50
4	Me	Me	Ar	Br	B	31	57
5	Me	Me	Ph	Br	B	30	72
6	Me	H	Ar	Br	B	32	72
7	CH_2Ph	Et	Et	OAc	A	33	69
8	CH_2Ph	R′/R″ = pyrrolidine		OAc	A	34	60
9	CH_2Ph	H	CH_2Ph	OAc	A	35	13
10	CH_2Ph	H	tBu	OAc	A	36	0[c]

[a] Ar = 2-*tert*-butylphenyl. [b] See Experimental section for descriptions of Methods A and B. [c] No reduction observed, see text.

ments were frequently assisted by obtaining ^{1}H–^{1}H COSY and ^{1}H–^{13}C COSY spectra, which were recorded on a JEOL EX 270 spectrometer. Reaction progress was monitored by thin layer chromatography (TLC) using Merck silica gel 60 F_{254} precoated plates which were visualised with ultraviolet light and developed by staining with either basic potassium permanganate solution or acidic ammonium molybdate(IV). Liquid chromatography was performed using forced flow (flash chromatography) with the indicated solvent system on Fluka silica gel 60 (220–440 mesh).

Organic solvents and reagents were dried from the following as required: THF and Et_2O (sodium–benzophenone ketyl), methanol (from magnesium methoxide onto 3 Å molecular sieves), CH_2Cl_2 and chlorotrimethylsilane (calcium hydride). Petroleum ether refers to light petroleum (bp 40–60 °C) which was distilled prior to use. All other reagents were used as received from commercial suppliers unless otherwise stated.

Synthesis of *N*-2-*tert*-butylphenyl-*N*-(2-methoxyethoxymethyl)-propionamide 10

(i) *N*-(2-*tert*-Butylphenyl)propionamide. Propionyl chloride (4.00 g, 43.23 mmol) was added dropwise to a stirred solution of 2-*tert*-butylaniline (7.10 g, 47.55 mmol) and NaOH (1.90 g, 47.55 mmol), in Et_2O (200 ml) and water (200 ml) at 0 °C, followed by warming to room temperature for 2 h. The reaction mixture was poured onto 2 M NaOH (50 ml) and extracted with Et_2O (3 × 50 ml), the combined organic extracts were washed with brine (50 ml), dried ($MgSO_4$) and evaporated under reduced pressure. The resulting white solid was recrystallised from light petroleum to give the desired amide as a white crystalline solid (7.88 g, 38.38 mmol, 89%), mp 119–120 °C (Found: C, 76.24; H, 9.40; N, 6.67. $C_{13}H_{19}NO$ requires C, 76.10; H, 9.26; N, 6.83%); ν_{max} ($CHCl_3$)/cm^{-1} 3467, 1681, 1578, 1493, 1365, 1293, 1091; δ_H (270 MHz, $CDCl_3$) 1.28 (3H, t, *J* 7.3, C*H*$_3$CH$_2$), 1.40 (9H, s, (C*H*$_3$)$_3$C), 2.42 (2H, q, *J* 7.3, CH$_3$C*H*$_2$), 7.21 (3H, m, Ar*H* and N*H*), 7.38 (1H, d, *J* 7.3, Ar*H*), 7.54 (1H, d, *J* 7.3, Ar*H*); δ_C (68 MHz, $CDCl_3$) 9.6 (CH_3), 30.4 (CH_2), 30.6 (CH_3), 34.5 (C), 126.1 (CH), 126.4 (CH), 126.5 (CH), 128.6 (CH), 135.1 (C), 143.1 (C), 172.2 (C=O); *m*/*z* (EI) 205 (M^+, 55%), 148 (100), 134 (100), 106 (24), 91 (23).

(ii) *N*-2-*tert*-Butylphenyl-*N*-(2-methoxyethoxymethyl)propionamide 10. To a stirred suspension of NaH (1.22 g of a 60% dispersion in oil, 30.39 mmol) in THF (10 ml) at 0 °C, under an atmosphere of nitrogen, was added dropwise a solution of the anilide prepared as described above (2.08 g, 10.13 mmol) in THF (10 ml), with vigorous evolution of hydrogen. After 15 min MEMCl (2.89 ml, 25.33 mmol) was added in one portion and the reaction mixture was stirred at 0 °C for 1 h. MeOH (5 ml) was then cautiously added and the reaction mixture poured onto water (50 ml) and extracted with EtOAc (3 × 50 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to yield a pale yellow oil that was subsequently purified by bulb to bulb distillation (160 °C/1 mmHg) to give **10** as a pale yellow oil (2.61 g, 8.90 mmol, 88%); ν_{max} (film)/cm^{-1} 2967, 1673, 1598, 1488, 1242, 1081, 761; δ_H (400 MHz, $CDCl_3$) 1.06 (3H, t, *J* 7.4, C*H*$_3$CH$_2$), 1.32 (9H, s, (C*H*$_3$)$_3$C), 2.03 (2H, m, CH$_3$C*H*$_2$), 3.38 (3H, s, C*H*$_3$O), 3.56 (2H, m, C*H*$_2$OCH$_3$), 3.77 (1H, ddd, *J* 9.1, 5.6, 3.4, NCH$_2$OC*H*$_2$), 3.85 (1H, ddd, *J* 9.1, 5.6, 3.4, NCH$_2$OC*H*$_2$), 4.36 (1H, d, *J* 10.0, NC*H*$_2$O), 5.81 (1H, d, *J* 10.0, NC*H*$_2$O), 7.12 (1H, d, *J* 7.7, Ar*H*), 7.22 (1H, dd, *J* 7.7, 7.7, Ar*H*), 7.33 (1H, dd, *J* 7.7, 7.7, Ar*H*), 7.54 (1H, d, *J* 7.7, Ar*H*); δ_C (68 MHz, $CDCl_3$) 8.9 (CH_3), 28.6 (CH_2), 32.0 (CH_3), 35.9 (C), 58.8 (CH_3), 68.8 (CH_2), 71.7 (CH_2), 78.2 (CH_2), 126.8 (CH), 128.5 (CH), 129.5 (CH), 132.3 (CH), 138.8 (C), 145.6 (C), 175.8 (C=O); *m*/*z* (EI) 236 ($M^+ - {}^t$Bu, 100%), 178 (18), 162 (45), 146 (38), 89 (86) (Found $M^+ - {}^t$Bu, 236.1286. $C_{17}H_{27}NO_3 - {}^t$Bu requires *M*, 236.1287).

Typical procedure for enolate reactions of 10: benzylation of 10 to give (R_a*,2*S**)-*N*-(2-*tert*-butylphenyl)-*N*-(2-methoxyethoxymethyl)-2-methyl-3-phenylpropionamide 11 (R = Bn)

^{n}BuLi (0.81 ml of a 1.60 M solution in hexanes, 1.30 mmol) was added in one portion to a stirred solution of diisopropylamine (0.20 ml, 1.50 mmol) in THF (10 ml) at −78 °C, under an atmosphere of nitrogen, followed by warming to 0 °C for 15 min. To the resulting solution of LDA at −78 °C, a solution of the anilide (293 mg, 1.00 mmol) in THF (1 ml) was added dropwise. After 30 min benzyl bromide (0.24 ml, 2.00 mmol) was added in one portion and the reaction mixture stirred for 30 min at −78 °C, followed by addition of saturated aqueous $NaHCO_3$ (2.5 ml) and then warming to room temperature. The reaction mixture was extracted with Et_2O (3 × 30 ml), the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (10 ml), brine (30 ml), dried ($MgSO_4$) and evaporated under reduced pressure. The resulting yellow oil was purified by column chromatography (20% EtOAc–light petroleum) to yield the *title compound* as a pale yellow oil (340 mg, 0.89 mmol, 89%) (Found: C, 75.41; H, 9.01; N, 3.53. $C_{24}H_{33}NO_3$ requires C, 75.16; H, 8.67; N, 3.65%); ν_{max} ($CHCl_3$)/cm^{-1} 2931, 1657, 1602, 1488, 1364, 1099, 908; δ_H (250 MHz, $CDCl_3$) 0.98 (3H, t, *J* 6.1, C*H*$_3$CH), 1.32 (9H, s, (C*H*$_3$)$_3$C), 2.48 (2H, m, PhC*H*$_2$), 3.05 (1H, m, CH$_3$C*H*), 3.38 (3H, s, C*H*$_3$O), 3.55 (2H, m, C*H*$_2$OCH$_3$), 3.81 (2H, m, NCH$_2$OC*H*$_2$), 4.39 (1H, d, *J* 10.0, NC*H*$_2$O), 5.82 (1H, d, *J* 10.0, NC*H*$_2$O), 6.76 (2H, m, Ar*H*), 7.02 (1H, dd, *J* 7.8, 1.5, Ar*H*), 7.15 (4H, m, Ar*H*), 7.37 (1H, ddd, *J* 7.8, 7.8, 1.5, Ar*H*), 7.56 (1H, dd, *J* 7.8, 1.5, Ar*H*); δ_C (68 MHz, $CDCl_3$) 15.3 (CH_3), 32.3 (CH_3), 36.1 (C), 39.6 (CH), 40.5 (CH_2), 58.8 (CH_3), 68.9 (CH_2), 71.8 (CH_2), 78.4 (CH_2), 126.1 (CH), 126.7 (CH), 128.0 (CH), 128.6 (CH), 128.9 (CH), 129.8 (CH), 132.5 (CH), 138.3 (C), 139.1 (C), 145.9 (C), 177.8 (C=O); *m*/*z* (EI) 326 ($M^+ - {}^t$Bu, 97%), 250 (10), 162 (20), 146 (42), 119 (45), 89 (100).

Allylation of 10 to give (R_a*,2*S)-*N*-(2-*tert*-butylphenyl)-*N*-(2-methoxyethoxymethyl)-2-methylpent-4-enamide 11 (R = allyl).** Reaction of **10** according to the procedure described above gave a crude product as a pale yellow oil, which was purified by flash column chromatography (20% EtOAc–light petroleum) to give the title compound as a colourless oil (250 mg, 75%) (Found: C, 71.95; H, 9.74; N, 4.08. $C_{20}H_{31}NO_3$ requires C, 72.04; H, 9.37; N, 4.20%); ν_{max} (film)/cm^{-1} 2971, 1666, 1598, 1488, 1088, 914, 733; δ_H (400 MHz, $CDCl_3$) 1.04 (3H, d, *J* 6.5, C*H*$_3$CH), 1.31 (9H, s, (C*H*$_3$)$_3$C), 2.18 (1H, m, CH$_3$C*H*), 2.34 (2H, m, C*H*$_2$CH=CH$_2$), 3.34 (3H, s, C*H*$_3$O), 3.55 (2H, m, C*H*$_2$OCH$_3$), 3.76 (1H, ddd, *J* 9.1, 5.6, 3.4, NCH$_2$OC*H*$_2$), 3.88 (1H, ddd, *J* 9.1, 5.6, 3.4, NCH$_2$OC*H*$_2$), 4.36 (1H, d, *J* 10.0, NC*H*$_2$O), 4.92 (2H, m, CH$_2$CH=C*H*$_2$), 5.51 (1H, m, CH$_2$C*H*=CH$_2$), 5.80 (1H, d, *J* 10.0, NC*H*$_2$O), 7.30 (3H, m, Ar*H*), 7.53 (1H, d, *J* 7.8, Ar*H*); δ_C (68 MHz, $CDCl_3$) 15.1 (CH_3), 32.2 (CH_3), 36.9 (C), 38.5 (CH_2), 58.7 (CH_3), 68.8 (CH_2), 71.7 (CH_2), 78.2 (CH_2), 116.7 (CH_2), 128.4 (CH), 128.5 (CH), 129.6 (CH), 132.4 (CH), 135.1 (CH), 138.3 (CH), 145.6 (C), 177.7 (C=O); *m*/*z* (EI) 276 ($M^+ - {}^t$Bu, 100%), 258 (10), 228 (18), 178 (23), 162 (71), 146 (98).

Alkylation of 10 with EtI to give (R_a*,2*S)-*N*-(2-*tert*-butylphenyl)-*N*-(2-methoxyethoxymethyl)-2-methylbutanamide 11 (R = ethyl).** Reaction of **10** according to the procedure described above gave a crude product as a pale yellow oil, which was purified by flash column chromatography (20% EtOAc–light petroleum) to give the title compound as a colourless oil (285 mg, 89%) (Found: C, 70.89; H, 9.92; N, 4.25. $C_{19}H_{31}NO_3$ requires C, 70.99; H, 9.72; N, 4.36%); ν_{max} (film)/cm^{-1} 2966, 1667, 1489, 1089, 761; δ_H (400 MHz, $CDCl_3$) 0.65 (3H, t, *J* 6.6, C*H*$_3$CH$_2$), 0.99 (3H, d, *J* 6.5, C*H*$_3$CH), 1.27 (9H, s, (C*H*$_3$)$_3$C), 1.55 (1H, m, CH$_3$C*H*$_2$), 2.05 (1H, m, CH$_3$C*H*$_2$), 3.31 (3H, s, C*H*$_3$O), 3.49 (2H, m, C*H*$_2$OCH$_3$), 3.70 (1H, ddd, *J* 9.0, 5.6, 3.4,

NCH_2OCH_2), 3.80 (1H, ddd, *J* 9.0, 5.6, 3.4, NCH_2OCH_2), 4.28 (1H, d, *J* 10.0, NCH_2O), 5.72 (1H, d, *J* 10.0, NCH_2O), 7.12 (2H, m, Ar*H*), 7.24 (1H, m, Ar*H*), 7.47 (1H, d, *J* 7.8, Ar*H*); δ_C (68 MHz, $CDCl_3$) 11.2 (CH_3), 14.9 (CH_3), 27.3 (CH_2), 32.3 (CH_3), 36.0 (C), 38.4 (CH_2), 58.8 (CH_3), 68.8 (CH_2), 71.7 (CH_2), 78.3 (CH_2), 126.5 (CH), 128.4 (CH), 129.5 (CH), 132.4 (CH), 138.5 (C), 145.7 (C), 178.5 (C=O); *m*/*z* (EI) 264 ($M^+ - {}^t$Bu, 82%), 146 (55), 89 (100), 59 (85), 57 (67).

Reaction of 10 with cinnamyl chloride to give (*R*$_a$*,2*S)-*N*-(2-*tert*-butylphenyl)-*N*-(2-methoxyethoxymethyl)-2-methyl-5-phenylpent-4-enamide 11 (R = cinnamyl).** Reaction of **10** according to the procedure described above gave a crude product as a pale yellow oil, which was purified by column chromatography (30% EtOAc–light petroleum) to yield the *title compound* as a yellow oil (300 mg, 0.73 mmol, 69%), bp 220 °C/0.3 mmHg (Found: C, 76.10; H, 8.85; N, 3.40. $C_{26}H_{35}NO_3$ requires C, 76.25; H, 8.61; N, 3.42%); ν_{max} (film)/cm^{-1} 3058, 3024, 2967, 1666, 1597, 1488, 1440, 1380, 1235, 1088, 761, 694; δ_H (500 MHz, $CDCl_3$) 1.11 (3H, d, *J* 6.5, CH_3CH), 1.33 (9H, s, $(CH_3)_3C$), 2.21 (1H, m, CH_3CH), 2.40 (1H, m, $CHCH_2$), 2.53 (1H, m, $CHCH_2$), 3.32 (3H, s, CH_3O), 3.47 (2H, m, CH_2OCH_3), 3.75 (1H, ddd, *J* 11.1, 6.1, 3.2, NCH_2OCH_2), 3.84 (1H, ddd, *J* 11.1, 6.1, 3.2, NCH_2OCH_2), 4.37 (1H, d, *J* 10.1, NCH_2O), 5.81 (1H, d, *J* 10.1, NCH_2O), 5.93 (1H, m, CH_2CHCH), 6.29 (1H, d, *J* 15.7, CH_2CHCH), 7.26 (8H, m, Ar*H*), 7.55 (1H, dd, *J* 8.1, 1.0, Ar*H*); δ_C (68 MHz, $CDCl_3$) 16.1 (CH_3), 32.5 (CH_3), 36.2 (C), 37.6 (CH), 38.3 (CH_2), 58.9 (CH_3), 68.9 (CH_2), 71.7 (CH_2), 78.4 (CH_2), 125.9 (CH), 126.6 (CH), 127.1 (CH), 127.2 (CH), 128.4 (CH), 128.6 (CH), 129.9 (CH), 131.9 (CH), 132.8 (CH), 137.1 (C), 138.3 (C) 145.9 (C), 177.8 (C=O); *m*/*z* (EI) 409 (M^+, 3%), 352 (8), 276 (100) (Found M^+, 409.2608. $C_{26}H_{35}NO_3$ requires *M*, 409.2617).

Sulfenylation of 10 using $PhSSO_2Ph$ to give (*R*$_a$*,2*S)-*N*-(2-*tert*-butylphenyl)-*N*-(2-methoxyethoxymethyl)-2-(phenylsulfenyl)propionamide 11 (R = SPh).** Reaction of **10** according to the procedure described above gave a crude product as a pale yellow oil, which was purified by column chromatography (30% EtOAc–light petroleum) to yield the *title compound* as a yellow oil (337 mg, 84%), bp 220 °C/0.3 mmHg (Found: C, 68.98; H, 8.04; N, 3.71. $C_{23}H_{31}NO_3S$ requires C, 68.79; H, 7.78; N, 3.49%); ν_{max} (film)/cm^{-1} 3059, 2966, 1668, 1597, 1487, 1440, 1373, 1243, 1083, 760, 692; δ_H (400 MHz, $CDCl_3$) 1.31 (9H, s, $(CH_3)_3C$), 1.37 (3H, d, *J* 6.7, CH_3CH), 3.40 (3H, s, CH_3O), 3.45 (1H, q, *J* 6.7, CH_3CH), 3.60 (2H, m, CH_2OCH_3), 3.75 (1H, ddd, *J* 11.1, 6.1, 3.2, NCH_2OCH_2), 4.05 (1H, ddd, *J* 11.1, 6.1, 3.2, NCH_2OCH_2), 4.43 (1H, d, *J* 10.1, NCH_2O), 5.83 (1H, d, *J* 10.1, NCH_2O), 7.14–7.54 (9H, m, Ar*H*); δ_C (68 MHz, $CDCl_3$) 17.4 (CH_3), 32.2 (CH_3), 35.8 (C), 43.8 (CH), 58.8 (CH_3), 68.8 (CH_2), 71.7 (CH_2), 78.4 (CH_2), 126.6 (CH), 127.7 (CH), 128.5 (CH), 128.7 (CH), 129.0 (CH), 132.5 (C), 133.1 (CH), 133.2 (CH), 137.6 (C) 145.6 (C), 173.2 (C=O); *m*/*z* (EI) 401 (M^+, 3%), 344 (54), 181 (17), 146 (14), 137 (48), 109 (20), 89 (100) (Found M^+, 401.2016. $C_{23}H_{31}NO_3S$ requires *M*, 401.2025).

Aldol reaction of 10 with benzaldehyde to give (*R*$_a$*,2*S,3*R**)-*N*-(2-*tert*-butylphenyl)-*N*-(2-methoxyethoxymethyl)-3-hydroxy-2-methyl-3-phenylpropionamide 14 (R = Ph).** Reaction of **10** according to the procedure described above gave a crude product as a pale yellow oil, which was purified by column chromatography (20% EtOAc–light petroleum) to yield the *title compound* as white crystals (320 mg, 0.80 mmol, 80%), mp 79–81 °C (Found: C, 72.25; H, 8.62; N, 3.43. $C_{24}H_{33}NO_4$ requires C, 72.15; H, 8.33; N, 3.51%); ν_{max} ($CHCl_3$)/cm^{-1} 3494, 2929, 2861, 1640, 1488, 1458, 1364, 1101; δ_H (250 MHz, $CDCl_3$) 0.90 (3H, d, *J* 6.8, CH_3CH), 1.32 (9H, s, $(CH_3)_3C$), 2.62 (1H, qd, *J* 6.8, 2.1, CH_3CH), 3.33 (3H, s, CH_3O), 3.55 (2H, m, CH_2OCH_3), 3.75 (1H, br s, PhCHO*H*), 3.87 (2H, m, NCH_2OCH_2), 4.46 (1H, d, *J* 10.0, NCH_2O), 5.07 (1H, br s, PhC*H*OH), 5.84 (1H, d, *J* 10.0, NCH_2O), 7.30 (9H, m, Ar*H*); δ_C (68 MHz, $CDCl_3$) 8.7 (CH_3), 32.4 (CH_3), 36.2 (C), 43.4 (CH), 58.9 (CH_3), 69.4 (CH_2), 71.9 (CH_2), 72.5 (CH), 78.6 (CH_2), 125.5 (CH), 126.9 (CH), 127.9 (CH), 129.0 (CH), 130.2 (CH), 132.4 (CH), 138.1 (C), 141.1 (C), 146.0 (C), 178.2 (C=O); *m*/*z* (EI) 342 ($M^+ - {}^t$Bu, 56%), 266 (11), 236 (39), 217 (23), 190 (9), 146 (100).

Aldol reaction of 10 with isobutyraldehyde to give (*R*$_a$*,2*S,3*R**)-*N*-(2-*tert*-butylphenyl)-*N*-(2-methoxyethoxymethyl)-3-hydroxy-2,4-dimethylpentanamide 14 (R = isopropyl).** Reaction of **10** according to the procedure described above gave a crude product as a pale yellow oil, which was purified by column chromatography (30% EtOAc–light petroleum) to yield the *title compound* as a yellow oil (330 mg, 0.90 mmol, 85%), bp 220 °C/0.3 mmHg (Found: C, 69.24; H, 9.99; N, 3.72. $C_{21}H_{35}NO_4$ requires C, 69.01; H, 9.65; N, 3.83%); ν_{max} ($CHCl_3$)/cm^{-1} 3447, 2928, 2874, 1640, 1598, 1488, 1459, 1364, 1093, 980; δ_H (500 MHz, $CDCl_3$) 0.28 (3H, d, *J* 6.6, $(CH_3)_2CH$), 0.96 (3H, d, *J* 6.6, $(CH_3)_2CH$), 1.02 (3H, d, *J* 6.8, CH_3CH), 1.34 (9H, s, $(CH_3)_3C$), 1.52 (1H, m, $(CH_3)_2CH$), 2.62 (1H, dq, *J* 6.8, 1.2, CH_3CH), 3.32 (1H, dd, *J* 9.4, 1.2, C*H*OH), 3.38 (3H, s, CH_3O), 3.57 (2H, m, CH_2OCH_3), 3.79 (1H, ddd, *J* 11.2, 5.6, 3.2, NCH_2OCH_2), 3.90 (1H, ddd, *J* 11.2, 5.6, 3.2, NCH_2OCH_2), 4.42 (1H, d, *J* 10.0, NCH_2O), 5.78 (1H, d, *J* 10.0, NCH_2O), 7.18 (1H, dd, *J* 8.0, 1.6, Ar*H*), 7.22 (1H, ddd, *J* 8.0, 7.3, 1.6, Ar*H*), 7.33 (1H, ddd, *J* 8.0, 7.3, 1.6, Ar*H*), 7.56 (1H, dd, *J* 8.0, 1.6, Ar*H*); δ_C (126 MHz, $CDCl_3$) 8.4 (CH_3), 17.9 (CH), 19.9 (CH_3), 30.4 (CH), 32.5 (CH_3), 36.2 (C), 37.9 (CH), 58.9 (CH_3), 69.4 (CH_2), 71.9 (CH_2), 78.5 (CH_2), 127.1 (CH), 128.9 (CH), 130.0 (CH), 132.6 (CH), 138.0 (C), 145.8 (C), 179.1 (C=O); *m*/*z* (EI) 308 ($M^+ - {}^t$Bu, 32%), 232 (20), 162 (29), 146 (100), 89 (24) (Found $M^+ - {}^t$Bu, 308.1852. $C_{21}H_{35}NO_4 - {}^t$Bu requires *M*, 308.1862).

Aldol reaction of 10 with pivaldehyde to give (*R*$_a$*,2*S,3*R**)-*N*-(2-*tert*-butylphenyl)-*N*-(2-methoxyethoxymethyl)-3-hydroxy-2,4,4-trimethylpentanamide 14 (R = *tert*-butyl).** Reaction of **10** according to the procedure described above gave a crude product as a pale yellow oil, which was purified by column chromatography (35% EtOAc–light petroleum) to yield the *title compound* as a pale yellow oil (330 mg, 0.87 mmol, 87%), bp 220 °C/0.3 mmHg (Found: C, 69.80; H, 10.07; N, 3.56. $C_{22}H_{37}NO_4$ requires C, 69.62; H, 9.83; N, 3.66%); ν_{max} (film)/cm^{-1} 3478, 2912, 2864, 1731, 1631, 1598, 1571, 1488, 1459, 1363, 1316; δ_H (500 MHz, $CDCl_3$) 0.71 (9H, s, $(CH_3)_3CCHOH$), 1.10 (3H, d, *J* 6.7, CH_3CH), 1.34 (9H, s, $(CH_3)_3C$), 2.72 (1H, q, *J* 6.7, CH_3CH), 3.38 (3H, s, CH_3O), 3.47 (1H, s, C*H*OH), 3.56 (2H, m, CH_2OCH_3), 3.80 (1H, ddd, *J* 11.2, 6.0, 3.2, NCH_2OCH_2), 3.90 (1H, ddd, *J* 11.2, 6.0, 3.2, NCH_2OCH_2), 4.40 (1H, d, *J* 10.0, NCH_2O), 5.76 (1H, d, *J* 10.0, NCH_2O), 7.21 (2H, m, Ar*H*), 7.32 (1H, m, Ar*H*), 7.56 (1H, dd, *J* 8.2, 1.1, Ar*H*); δ_C (68 MHz, $CDCl_3$) 10.2 (CH_3), 26.8 (CH_3), 32.5 (CH_3), 35.3 (C), 36.2 (C), 37.4 (CH), 58.8 (CH_3), 69.3 (CH_2), 71.9 (CH_2), 77.2 (CH), 78.6 (CH_2), 126.8 (CH), 128.8 (CH), 130.0 (CH), 132.7 (CH), 138.0 (C), 145.8 (C), 179.6 (C=O); *m*/*z* (EI) 322 ($M^+ - {}^t$Bu, 32%), 246 (42), 236 (15) (Found $M^+ - {}^t$Bu, 322.2016. $C_{22}H_{37}NO_4 - {}^t$Bu requires *M*, 322.2018).

Aldol reaction of 10 with cyclohexanecarbaldehyde to give (*R*$_a$*,2*R,3*R**)-*N*-(2-*tert*-butylphenyl)-*N*-(2-methoxyethoxymethyl)-3-cyclohexyl-3-hydroxy-2-methylpropionamide 14 (R = cyclohexyl).** Reaction of **10** according to the procedure described above gave a crude product as a pale yellow oil, which was purified by column chromatography (25% EtOAc–light petroleum) to yield the *title compound* as a yellow oil (360 mg, 0.89 mmol, 89%), bp 220 °C/0.3 mmHg (Found: C, 71.27; H, 9.98; N, 3.37. $C_{24}H_{39}NO_4$ requires C, 71.07; H, 9.69; N, 3.45%); ν_{max} (film)/cm^{-1} 3454, 2924, 2851, 1642, 1598, 1488, 1442, 1363, 1233, 1091, 761; δ_H (500 MHz, $CDCl_3$) 0.26 (1H, m,

$(CH_2)_5CH$), 1.01 (3H, d, *J* 6.8, CH_3CH), 1.16 (10H, m, $(CH_2)_5$), 1.33 (9H, s, $(CH_3)_3C$), 2.60 (1H, q, *J* 6.8, CH_3CH), 3.38 (1H, m, CHOH), 3.38 (3H, s, CH_3O), 3.56 (2H, m, CH_2OCH_3), 3.79 (1H, ddd, *J* 11.1, 5.6, 3.1, NCH_2OCH_2), 3.89 (1H, ddd, *J* 11.1, 5.6, 3.1, NCH_2OCH_2), 4.41 (1H, d, *J* 10.2, NCH_2O), 5.79 (1H, d, *J* 10.2, NCH_2O), 7.16 (1H, dd, *J* 7.7, 1.3, ArH), 7.22 (1H, ddd, *J* 7.7, 7.5, 1.3, ArH), 7.33 (1H, ddd, *J* 7.7, 7.5, 1.3, ArH), 7.55 (1H, dd, *J* 7.7, 1.3, ArH); δ_C (126 MHz, $CDCl_3$) 8.6 (CH_3), 25.8 (CH_2), 26.2 (CH_2), 27.8 (CH_2), 30.2 (CH_2), 32.6 (CH_3), 36.3 (C), 37.4 (CH), 39.8 (CH), 59.0 (CH_3), 60.4 (CH_2), 69.5 (CH_2), 72.0 (CH_2), 75.2 (CH), 78.6 (CH_2), 127.2 (CH), 130.0 (CH), 131.3 (CH), 132.6 (CH), 138.1 (C), 145.9 (C), 179.2 (C=O); *m*/*z* (EI) 236 (M^+, 50%), 146 (100), 113 (82), 101 (51), 89 (76).

Aldol reaction of 10 with propanal to give (R_a*,2*S,3*R**)-*N*-(2-*tert*-butylphenyl)-*N*-(2-methoxyethoxymethyl)-3-hydroxy-2-methylpentanamide 14 (R = ethyl).** Reaction of **10** according to the procedure described above gave a crude product as a pale yellow oil, which was purified by column chromatography (25% EtOAc–light petroleum) to yield the *title compound* as a pale yellow oil (150 mg, 0.43 mmol, 86%), bp 200 °C/4 mmHg (Found: C, 68.19; H, 9.53; N, 3.77. $C_{20}H_{33}NO_4$ requires C, 68.34; H, 9.46; N, 3.98%); ν_{max} (film)/cm^{-1} 3463, 3063, 2959, 1644, 1598, 1571, 1488, 1456, 1409, 1325, 1300; δ_H (250 MHz, $CDCl_3$) 0.61 (3H, t, *J* 7.1, CH_3CH_2), 1.03 (3H, d, *J* 7.1, CH_3CH), 1.34 (9H, s, $(CH_3)_3C$), 2.44 (1H, m, CH_3CH), 3.38 (3H, s, CH_3O), 3.56 (2H, m, CH_2OCH_3), 3.81 (2H, m, NCH_2OCH_2), 4.41 (1H, d, *J* 10.0, NCH_2O), 5.81 (1H, d, *J* 10.0, NCH_2O), 7.26 (3H, m, ArH), 7.56 (1H, dd, *J* 8.0, 1.4, ArH); δ_C (68 MHz; $CDCl_3$) 8.3 (CH_3), 10.1 (CH_3), 26.0 (CH_2), 32.2 (CH_3), 35.9 (C), 39.5 (CH), 58.7 (CH_3), 68.8 (CH_2), 71.6 (CH_2), 72.3 (CH), 78.0 (CH_2), 126.6 (CH), 128.8 (CH), 129.6 (CH), 132.0 (CH), 137.6 (C), 145.3 (C), 180.4 (C=O); *m*/*z* (EI) 294 ($M^+ - {}^tBu$, 59%), 218 (54), 188 (18) (Found $M^+ - {}^tBu$, 294.1690. $C_{20}H_{33}NO_4 - {}^tBu$ requires *M*, 294.1705).

Reduction of racemic 11 (R = Bn) with $LiAlH_4$ to give 2-methyl-3-phenylpropan-1-ol (±)-17

To a stirred suspension of $LiAlH_4$ (273 mg, 7.20 mmol) in THF (40 ml) at −10 °C, under an atmosphere of nitrogen, was added the anilide **11** (R = Bn) (230 mg, 0.60 mmol) in THF (15 ml). The reaction mixture was stirred at room temperature for 24 h before cautiously adding 2 M NaOH (10 ml) and water (10 ml). The reaction mixture was filtered and extracted with Et_2O (3 × 30 ml), the combined organic extracts were washed with water (3 × 10 ml), brine (20 ml), dried ($MgSO_4$) and evaporated under reduced pressure. The crude mixture was purified by column chromatography (10% EtOAc–light petroleum) to give (±)-**17** as a pale yellow oil (72 mg, 0.48 mmol, 80%); ν_{max} (film)/cm^{-1} 3332, 3084, 3061, 3025, 2919, 1603, 1494, 1453, 1378; δ_H (250 MHz, $CDCl_3$) 0.90 (3H, d, *J* 6.7, CH_3CH), 1.81 (1H, s, CH_2OH), 1.93 (1H, m, CH_3CH), 2.40 (1H, dd, *J* 13.4, 8.1, $PhCH_2$), 2.75 (1H, dd, *J* 13.4, 8.1, $PhCH_2$), 3.48 (2H, m, CH_2OH), 7.23 (5H, m, ArH); δ_C (126 MHz, $CDCl_3$) 16.5 (CH_3), 37.8 (CH), 39.8 (CH_2), 67.7 (CH_2), 125.9 (CH), 128.3 (CH), 129.2 (CH), 140.7 (C); *m*/*z* (EI) 150 (M^+, 25%), 132 (20), 117 (50), 92 (53), 91 (100) (Found M^+, 150.1045. $C_{10}H_{14}O$ requires *M*, 150.1045).

Reduction of racemic 14 (R = Ph) with $LiAlH_4$ to give 2-methyl-1-phenylpropane-1,3-diol (±)-18

To a stirred suspension of $LiAlH_4$ (221 mg, 5.83 mmol) in THF (35 ml) under an atmosphere of nitrogen, was added the anilide **14** (R = Ph) (174 mg, 0.44 mmol) in THF (5 ml). The reaction mixture was stirred for 24 h before 2 M NaOH (2.5 ml) and H_2O (2.5 ml) were carefully added. The mixture was extracted with EtOAc (3 × 20 ml), the combined organic extracts were washed with water (20 ml), dried ($MgSO_4$), and evaporated under reduced pressure. The resulting yellow oil was purified by flash column chromatography (50% EtOAc–light petroleum) to give the *title compound* as a yellow oil (50 mg, 0.30 mmol, 68%); ν_{max} ($CHCl_3$)/cm^{-1} 3362, 2913, 1604, 1493, 1456; δ_H (500 MHz, $CDCl_3$) 0.84 (3H, d, *J* 7.0, CH_3CH), 2.07 (1H, m, CH_3CH), 2.39 (1H, s, CH_2OH), 2.90 (1H, s, PhCHOH), 3.67 (2H, m, CH_2OH), 4.94 (1H, s, PhCHOH), 7.27 (1H, m, PhH), 7.34 (4H, m, PhH); δ_C (126 MHz, $CDCl_3$) 10.8 (CH_3), 41.5 (CH), 66.5 (CH_2), 76.8 (CH), 126.2 (CH), 127.3 (CH), 128.2 (CH), 142.7 (C); *m*/*z* (EI) 166 (M^+, 4%), 148 (19), 107 (100) (Found M^+, 166.0997. $C_{10}H_{14}O_2$ requires *M*, 166.0994).

(2*S*)-2-Acetoxypropionic acid (−)-22[16]

To a stirred solution of (*S*)-lactic acid (3.68 g, 40.9 mmol) in AcOH (11.7 ml) under an atmosphere of nitrogen, was added acetyl chloride (8.71 ml, 122.6 mmol) slowly. The reaction mixture was stirred for 5 h before removing AcOH and acetyl chloride under reduced pressure. The crude oil was purified by bulb to bulb distillation (112 °C/2 mmHg) to afford (−)-**22** as a colourless viscous oil (4.88 g, 36.9 mmol, 90%), $[\alpha]_D^{23}$ −58 (*c* 6.70, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3512, 3176, 2900, 2638, 1732, 1460, 1374, 1287; δ_H (500 MHz, $CDCl_3$) 1.54 (3H, d, *J* 7.2, CH_3CH), 2.14 (3H, s, CH_3CO), 5.11 (1H, q, *J* 7.2, CH_3CH), 9.95 (1H, br s, CO_2H); δ_C (126 MHz, $CDCl_3$) 16.9 (CH_3), 20.7 (CH_3), 68.2 (CH), 170.6 (C=O), 176.7 (C=O); *m*/*z* (FAB) 133 (MH^+, 13%), 120 (11) (Found MH^+, 133.0510. $C_5H_8O_4$ requires *M*, 133.0501).

(2*S*)-*N*-(2-*tert*-Butylphenyl)-2-acetoxypropionamide (−)-23

To a stirred solution of the acid (−)-**22** (2.00 g, 15.14 mmol) and 2-*tert*-butylaniline (1.51 g, 10.09 mmol) in CH_2Cl_2 (10 ml) at 0 °C, under an atmosphere of nitrogen, was added EDC·HCl (2.90 g, 15.14 mmol) in one portion. The reaction mixture was stirred at room temperature for 24 h before pouring onto water (30 ml) and extracting with CH_2Cl_2 (3 × 10 ml), the combined organics were washed with saturated aqueous $NaHCO_3$ (3 × 10 ml), 2 M HCl (3 × 10 ml), brine (10 ml), dried ($MgSO_4$) and evaporated under reduced pressure to give a white solid. Recrystallising from EtOAc gave the *title compound* as white crystals (2.18 g, 8.28 mmol, 82%), mp 107–108 °C; $[\alpha]_D^{23}$ −33 (*c* 0.94, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3460, 2969, 2876, 1750, 1689, 1580, 1449, 1372; δ_H (500 MHz, $CDCl_3$) 1.43 (9H, s, $(CH_3)_3C$), 1.60 (3H, d, *J* 6.9, CH_3CH), 2.21 (3H, s, CH_3C=O), 5.42 (1H, q, *J* 6.9, CH_3CH), 7.16 (1H, td, *J* 7.9, 1.4, ArH), 7.25 (1H, m, ArH), 7.40 (1H, dd, *J* 7.9, 1.4, ArH), 7.79 (1H, dd, *J* 7.9, 1.4, ArH), 8.11 (1H, br s, NH); δ_C (126 MHz, $CDCl_3$) 18.0 (CH_3), 21.2 (CH_3), 30.6 (CH_3), 34.5 (C), 71.2 (CH), 126.1 (CH), 126.2 (CH), 126.6 (CH), 127.0 (CH), 134.5 (C), 141.3 (C), 168.2 (C), 168.2 (C=O), 170.9 (C=O); *m*/*z* (EI) 264 (MH^+, 20%), 263 (100), 206 (33), 176 (68), 160 (23), 149 (97) (Found M^+, 263.1517. $C_{15}H_{21}NO_3$ requires *M*, 263.1521).

***N*-Alkylation of (−)-23 to give atropisomeric derivatives (S_a,2*S*)-2-acetoxy-*N*-(2-*tert*-butylphenyl)-*N*-(2-methoxyethoxymethyl)-propionamide (+)-24a, and (R_a,2*S*)-2-acetoxy-*N*-(2-*tert*-butylphenyl)-*N*-(2-methoxyethoxymethyl)propionamide (−)-24b**

To a stirred suspension of NaH (202 mg of a 60% dispersion in oil, 5.05 mmol) in THF (50 ml) at 0 °C, under an atmosphere of nitrogen, was added dropwise a solution of the anilide (−)-**22** (1.40 g, 5.32 mmol) in THF (3 ml), with vigorous evolution of hydrogen. After 15 min stirring at room temperature, the reaction mixture was cooled to 0 °C before addition of MEMCl (0.55 ml, 4.79 mmol) in one portion. The reaction mixture was stirred at 0 °C for 1 h and then at room temperature overnight. MeOH (5 ml) was then cautiously added and the reaction mixture poured onto water (40 ml) and extracted with EtOAc (3 × 30 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced

pressure to yield a yellow oil that was subsequently purified by column chromatography (25% EtOAc–light petroleum) to give firstly the diastereomer (−)-**24b** (470 mg, 1.34 mmol, 25%) as a pale yellow oil, $[a]_D^{23}$ −60 (*c* 1.22, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2938, 2881, 1738, 1674, 1489, 1456, 1370; δ_H (500 MHz, $CDCl_3$) 1.28 (3H, d, *J* 6.5, C*H*$_3$CH), 1.33 (9H, s, (C*H*$_3$)$_3$C), 2.00 (3H, s, C*H*$_3$C=O), 3.38 (3H, s, C*H*$_3$O), 3.57 (2H, m, C*H*$_2$OCH$_3$), 3.77 (1H, ddd, *J* 11.1, 5.9, 3.3, NCH$_2$OC*H*$_2$), 3.94 (1H, ddd, *J* 11.1, 5.9, 3.3, NCH$_2$OC*H*$_2$), 4.44 (1H, d, *J* 10.1, NC*H*$_2$O), 5.06 (1H, q, *J* 6.5, CH$_3$C*H*), 5.82 (1H, d, *J* 10.1, NC*H*$_2$O), 7.19 (1H, m, Ar*H*), 7.25 (1H, dd, *J* 7.7, 1.5, Ar*H*), 7.33 (1H, td, *J* 7.7, 1.5, Ar*H*), 7.54 (1H, dd, *J* 7.7, 1.5, Ar*H*); δ_C (126 MHz, $CDCl_3$) 15.8 (CH_3), 20.8 (CH_3), 32.6 (CH_3), 36.3 (C), 59.1 (CH_3), 67.9 (CH), 69.1 (CH_2), 72.0 (CH_2), 79.0 (CH_2), 126.6 (CH), 129.2 (CH), 131.3 (CH), 132.8 (CH), 136.9 (C), 145.9 (C), 169.7 (C=O), 171.4 (C=O); *m*/*z* (EI) 294 (M$^+$ − ^{t}Bu, 50%), 263 (4) (Found M$^+$ − ^{t}Bu, 294.1329. $C_{19}H_{29}NO_5$ − ^{t}Bu requires *M*, 294.1342), followed by (+)-**24a** (760 mg, 2.16 mmol, 41%) as a pale yellow oil, $[a]_D^{23}$ +21 (*c* 1.36, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2931, 2882, 2822, 1733, 1682, 1488, 1456, 1371; δ_H (500 MHz, $CDCl_3$) 1.32 (9H, s, (C*H*$_3$)$_3$C), 1.36 (3H, d, *J* 6.5, C*H*$_3$CH), 2.04 (3H, s, C*H*$_3$C=O), 3.38 (3H, s, C*H*$_3$O), 3.58 (2H, m, C*H*$_2$OCH$_3$), 3.78 (1H, ddd, *J* 11.2, 5.8, 3.4, NCH$_2$OC*H*$_2$), 3.86 (1H, ddd, *J* 11.2, 5.8, 3.4, NCH$_2$OC*H*$_2$), 4.38 (1H, d, *J* 10.0, NC*H*$_2$O), 5.11 (1H, q, *J* 6.5, CH$_3$C*H*), 5.82 (1H, d, *J* 10.0, NC*H*$_2$O), 7.19 (2H, m, Ar*H*), 7.36 (1H, td, *J* 7.9, 1.3, Ar*H*), 7.57 (1H, dd, *J* 7.9, 1.3, Ar*H*); δ_C (126 MHz, $CDCl_3$) 18.2 (CH_3), 21.0 (CH_3), 32.2 (CH_3), 36.3 (C), 59.0 (CH_3), 68.0 (CH), 69.3 (CH_2), 71.9 (CH_2), 79.0 (CH_2), 126.9 (CH), 129.3 (CH), 130.4 (CH), 132.7 (CH), 137.0 (C), 146.3 (C), 169.8 (C=O), 172.2 (C=O); *m*/*z* (EI) 294 (M$^+$ − ^{t}Bu, 44%), 252 (8), 221 (4) (Found M$^+$ − ^{t}Bu, 294.1340. $C_{19}H_{29}NO_5$ − ^{t}Bu requires *M*, 294.1342).

Typical conditions for SmI_2 reduction in the presence of LiCl (Method A in Table 3): conversion of (+)-24a and (−)-24b into (+)-10 and (−)-10 respectively

A solution of flame-dried LiCl (1.06 g, 24.96 mmol) in THF (24 ml) was added to a solution of SmI_2 in THF (40 ml), freshly prepared from Sm metal (1.38 g, 9.15 mmol) and 1,2-diiodoethane (2.35 g, 8.32 mmol). After 30 min, a solution of the starting anilide (−)-**24b** (450 mg, 1.28 mmol) in THF (2 ml) was added and the reaction mixture stirred for 24 h. The reaction mixture was then poured onto saturated aqueous Na_2SO_3 (50 ml) and the organics extracted with EtOAc (2 × 50 ml), washed with saturated aqueous Na_2SO_3 (50 ml), brine (50 ml), dried ($MgSO_4$) and solvent removed under reduced pressure. The crude oil was purified by column chromatography (30% EtOAc–light petroleum) to give (−)-**10** as a pale yellow oil (277 mg, 0.94 mmol, 73%), $[a]_D^{23}$ −26 (*c* 1.04, $CHCl_3$). An analogous reaction using (+)-**24a** gave (+)-**10** in 65% yield as a pale yellow oil, $[a]_D^{23}$ +26 (*c* 2.34, $CHCl_3$). Spectroscopic data were in accord with those obtained for the racemic material, listed above.

Methylation of (+)-10 and (−)-10 for purposes of determination of enantiomeric excess: synthesis of *N*-(2-*tert*-butylphenyl)-*N*-(2-methoxyethoxymethyl)isobutyramides 25

To a stirred solution of diisopropylamine (0.10 ml, 0.75 mmol) in THF (5 ml) at −78 °C, under an atmosphere of nitrogen, was added ^{n}BuLi (0.50 ml of a 1.3 M solution in hexanes, 0.65 mmol), followed by warming to 0 °C for 15 min. To the resulting solution of LDA at −78 °C, a solution of the anilide (+)-**10** (147 mg, 0.50 mmol) in THF (1 ml), was added dropwise. After 30 min MeI (0.06 ml, 1.00 mmol) was added in one portion and the reaction mixture stirred at −78 °C for 30 min, saturated aqueous $NaHCO_3$ (2.5 ml) was then added and the reaction mixture allowed to warm to room temperature. The reaction mixture was extracted with EtOAc (3 × 10 ml), the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (10 ml), brine (10 ml), dried ($MgSO_4$), and evaporated under reduced pressure. The resulting yellow oil was purified by flash column chromatography (30% EtOAc–light petroleum) and then bulb to bulb distillation (bp 220 °C/0.8 mmHg) to give **25** as a yellow oil (130 mg, 0.42 mmol, 84%); ν_{max} (film)/cm^{-1} 2968, 2875, 1667, 1488, 1470, 1441, 1402, 1384, 1361; δ_H (250 MHz, $CDCl_3$) 1.11 (3H, d, *J* 3.1, (C*H*$_3$)$_2$CH), 1.14 (3H, d, *J* 3.1, (C*H*$_3$)$_2$CH), 1.38 (9H, s, (C*H*$_3$)$_3$C), 2.40 (1H, m, (CH$_3$)$_2$C*H*), 3.44 (3H, s, C*H*$_3$O), 3.62 (2H, m, C*H*$_2$OCH$_3$), 3.84 (1H, ddd, *J* 11.1, 5.4, 3.7, NCH$_2$OC*H*$_2$), 3.93 (1H, ddd, *J* 11.1, 5.4, 3.7, NCH$_2$OC*H*$_2$), 4.41 (1H, d, *J* 10.1, NC*H*$_2$O), 5.87 (1H, d, *J* 10.1, NC*H*$_2$O), 7.34 (3H, m, Ar*H*), 7.61 (1H, dd, *J* 7.6, 1.1, Ar*H*); δ_C (68 MHz, $CDCl_3$) 18.3 (CH_3), 20.6 (CH_3), 32.3 (CH_3), 36.1 (C), 58.9 (CH_3), 68.9 (CH_2), 71.9 (CH_2), 78.3 (CH_2), 126.7 (CH), 128.6 (CH), 129.6 (CH), 132.3 (CH), 138.7 (C), 145.8 (C), 179.4 (C=O); *m*/*z* (EI) 250 (M$^+$ − ^{t}Bu, 100%), 146 (43) (Found M$^+$ − ^{t}Bu, 250.1451. $C_{18}H_{29}NO_3$ − ^{t}Bu requires *M*, 250.1443).

An analogous reaction using the anilide (−)-**10** gave the enantiomeric product **25** with corresponding spectroscopic data.

HPLC analysis of samples of **25** was carried out using a Chiralcel OD column, employing hexane–^{i}PrOH (99 : 1) as eluant. The two enantiomers showed baseline separation, with retention times of 10.5 and 12.5 minutes.

Polarimetric data for (+)-11, (−)-11, (+)-17 and (−)-17 (see Scheme 8)

Spectroscopic data for the conversions shown were in accord with those for racemic materials, given above.

The sequence starting with (+)-**10** gave benzylated amide (+)-**11**, $[a]_D^{23}$ +79 (*c* 0.73, $CHCl_3$), and then alcohol (−)-**17**, $[a]_D^{23}$ −10 (*c* 1.77, C_6H_6). Starting with (−)-**10** gave benzylated amide (−)-**11**, $[a]_D^{23}$ −80 (*c* 0.70, $CHCl_3$), and then alcohol (+)-**17**, $[a]_D^{23}$ +12 (*c* 0.5, C_6H_6). The literature value for (−)-**17**, established to be the (*S*)-enantiomer is $[a]_D$−11 (*c* 2.75, C_6H_6).[13]

Data for products of SmI_2 reductions (see Table 3)

Starting amides were prepared by standard techniques, principally utilising EDC-mediated coupling of appropriate carboxylic acids with amine partners. The α-bromo derivatives were made by Schotten–Baumann reactions using α-bromopropionyl chloride.

Reductions involving LiCl (Method A) were carried out as indicated above for (−)-**24b**. For Method B see typical procedure below.

Entry 1. Method A was used, giving a crude solid which was purified by column chromatography (20% EtOAc–light petroleum) to give **30** as white crystals (27 mg, 0.17 mmol, 85%), mp 55–56 °C (lit.,[17] 55–56 °C); ν_{max} ($CHCl_3$)/cm^{-1} 2981, 2940, 1644, 1596, 1496, 1463, 1389; δ_H (500 MHz, $CDCl_3$) 1.05 (3H, t, *J* 7.4, C*H*$_3$CH$_2$), 2.07 (2H, m, CH$_3$C*H*$_2$), 3.27 (3H, s, NC*H*$_3$), 7.19 (2H, m, Ph*H*), 7.33 (1H, app t, *J* 7.4, Ph*H*), 7.42 (2H, m, Ph*H*); δ_C (126 MHz, $CDCl_3$) 9.8 (CH_3), 27.6 (CH_2), 37.4 (CH_3), 127.4 (CH), 127.8 (CH), 129.8 (CH), 144.4 (C), 174.0 (C=O); *m*/*z* (EI) 163 (M$^+$, 26%), 107 (100), 106 (37) (Found M$^+$, 163.0997. $C_{10}H_{13}NO$ requires *M*, 163.0997).

Entry 2. Method A was used to give an oil which was purified by column chromatography (20% EtOAc–light petroleum) to give **10** as an oil (97 mg, 0.33 mmol, 69%), with spectroscopic data identical to those listed above.

Entry 3. Method A was used, giving a crude solid which was purified by column chromatography (15% EtOAc–light petroleum) to give **31** as a low melting point white solid (20 mg, 0.09 mmol, 50%), ν_{max} ($CHCl_3$)/cm^{-1} 2966, 1681, 1597, 1570, 1487, 1376, 1076; δ_H (400 MHz, $CDCl_3$) 1.04 (3H, t, *J* 7.4, C*H*$_3$CH$_2$), 1.37 (9H, s, (C*H*$_3$)$_3$C), 1.97 (2H, m, CH$_3$C*H*$_2$), 3.18

(3H, s, NCH_3), 6.96 (1H, dd, *J* 7.7, 1.5, Ar*H*), 7.22 (1H, ddd, *J* 7.7, 7.7, 1.5, Ar*H*), 7.32 (1H, ddd, *J* 7.7, 7.7, 1.5, Ar*H*), 7.54 (1H, dd, *J* 7.7, 1.5, Ar*H*); δ_C (68 MHz, $CDCl_3$) 9.1 (CH_3), 28.1 (CH_2), 31.6 (CH_3), 35.6 (C), 38.5 (CH_3), 127.3 (CH), 128.2 (CH), 129.1 (CH), 129.9 (CH), 141.8 (C), 146.0 (C), 174.7 (C=O); *m*/*z* (EI) 162 ($M^+ - {}^tBu$, 100%) (Found $M^+ - {}^tBu$, 162.0905. $C_{14}H_{21}NO - {}^tBu$ requires *M*, 162.0919).

Entry 4: typical Method B. To a solution of SmI_2 in THF (15 ml), freshly prepared from Sm metal (232 mg, 1.54 mmol) and 1,2-diiodoethane (395 mg, 1.40 mmol), was added a solution of the starting anilide (104 mg, 0.35 mmol) in THF (1 ml) and the reaction mixture stirred for 24 h. The reaction mixture was then poured onto saturated aqueous Na_2SO_3 (40 ml) and the organics extracted with EtOAc (2 × 40 ml), washed with saturated aqueous Na_2SO_3 (30 ml), brine (30 ml), dried ($MgSO_4$) and solvent removed under reduced pressure. The crude solid was purified by column chromatography (20% EtOAc–light petroleum) to give **31** (44 mg, 0.20 mmol, 57%), identical to entry 3.

Entry 5. Method B was used to give a crude solid which was purified by column chromatography (30% EtOAc–light petroleum) to give **30** (59 mg, 0.36 mmol, 72%), identical to entry 1.

Entry 6. Method B was used to give a crude solid which was purified by column chromatography (30% EtOAc–light petroleum) to give **32** as white crystals (74 mg, 0.36 mmol, 72%). For spectroscopic data, see preparation of **10**.

Entry 7. Method A was used to give a crude oil which was purified by column chromatography (40% EtOAc–light petroleum) to give **33** as a pale yellow oil (60 mg, 0.29 mmol, 69%);[18] ν_{max} ($CHCl_3$)/cm^{-1} 2937, 2876, 1650, 1488, 1455, 1383, 1363, 1312; δ_H (250 MHz, $CDCl_3$) 1.10 (6H, m, (CH_3CH$_2$)$_2$N), 2.59 (2H, m, PhCH$_2$CH_2), 2.98 (2H, t, *J* 7.9, PhCH_2CH$_2$), 3.22 (2H, q, *J* 7.1, (CH$_3$CH_2)$_2$N), 3.38 (2H, q, *J* 7.1, (CH$_3$CH_2)$_2$N), 7.24 (5H, m, Ph*H*); δ_C (68 MHz, $CDCl_3$) 13.0 (CH_3), 14.2 (CH_3), 31.6 (CH_2), 35.1 (CH_2), 40.2 (CH_2), 41.9 (CH_2), 126.0 (CH), 128.4 (CH), 141.5 (C), 171.2 (C=O); *m*/*z* (EI) 205 (M^+, 48%), 204 (22), 203 (58) (Found M^+, 205.1461. $C_{13}H_{19}NO$ requires *M*, 205.1467).

Entry 8. Method A was used to give a crude oil which was purified by column chromatography (60% EtOAc–light petroleum) to give **34** as a pale yellow oil (25 mg, 0.12 mmol, 60%);[19] ν_{max} ($CHCl_3$)/cm^{-1} 2950, 2876, 1722, 1644, 1495, 1456, 1344; δ_H (500 MHz, $CDCl_3$) 1.82 (4H, m, N(CH_2)$_4$), 2.55 (2H, t, *J* 7.9, PhCH$_2$CH_2), 2.97 (2H, t, *J* 7.9, PhCH_2CH$_2$), 3.26 (2H, t, *J* 6.6, N(CH_2)$_4$), 3.45 (2H, t, *J* 6.6, N(CH_2)$_4$), 7.22 (5H, m, Ph*H*); δ_C (126 MHz, $CDCl_3$) 24.2 (CH_2), 25.8 (CH_2), 31.0 (CH_2), 36.5 (CH_2), 45.5 (CH_2), 46.4 (CH_2), 125.8 (CH), 128.2 (CH), 141.2 (C), 170.6 (C=O); *m*/*z* (EI) 204 (MH^+, 11%), 203 (86), 131 (14), 112 (100), 105 (15) (Found M^+, 203.1306. $C_{13}H_{17}NO$ requires *M*, 203.1310).

Entry 9. Method A was used to give a mixture of products which were separated by column chromatography (40% EtOAc–light petroleum) to give firstly the undesired hydrolysis product, (*S*)-*N*-benzyl-2-hydroxy-3-phenylpropionamide, as a white solid (34 mg, 0.13 mmol, 65%), mp 81–82 °C; $[a]_D^{23}$ −57.7 (*c* 1.15, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3422, 2927, 1667, 1605, 1586, 1547, 1496, 1454; δ_H (500 MHz, $CDCl_3$) 2.60 (1H, d, *J* 4.5, O*H*), 2.93 (1H, dd, *J* 13.9, 6.4, PhCH_2), 3.25 (1H, dd, *J* 13.9, 6.4, PhCH_2), 4.34 (1H, m, PhCH$_2$C*H*), 4.39 (1H, dd, *J* 14.8, 5.9, PhCH_2N), 4.46 (1H, dd, *J* 14.8, 5.9, PhCH_2NH), 6.80 (1H, br s, N*H*), 7.18 (2H, m, Ph*H*), 7.27 (8H, m, Ph*H*); δ_C (126 MHz, $CDCl_3$) 41.0 (CH_2), 43.2 (CH_2), 73.0 (CH), 127.2 (CH), 127.6 (CH), 127.9 (CH), 128.8 (CH), 128.9 (CH), 129.7 (CH), 136.7 (C), 137.9 (C), 172.4 (C=O); *m*/*z* (EI) 255 (M^+, 10%), 238 (7), 237 (35), 164 (11) (Found M^+, 255.1263. $C_{16}H_{17}NO_2$ requires *M*, 255.1259), followed by *N*-benzyl-3-phenylpropionamide, **35**, as a white solid (6 mg, 0.025 mmol, 13%), mp 78–79 °C (lit.,[20] 83–84 °C); ν_{max} ($CHCl_3$)/cm^{-1} 2927, 2856, 1667, 1604, 1496, 1454; δ_H (500 MHz, $CDCl_3$) 2.52 (2H, t, *J* 7.6, PhCH_2), 3.00 (2H, t, *J* 7.6, PhCH$_2$CH_2), 4.40 (2H, d, *J* 5.7, PhCH_2N), 5.60 (1H, br s, N*H*), 7.15 (2H, m, Ph*H*), 7.22 (3H, m, Ph*H*), 7.28 (5H, m, Ph*H*); δ_C (126 MHz, $CDCl_3$) 31.8 (CH_2), 38.6 (CH_2), 43.7 (CH_2), 126.3 (CH), 127.5 (CH), 127.8 (CH), 128.5 (CH), 128.6 (CH), 128.7 (CH), 138.2 (C), 140.8 (C), 171.9 (C=O); *m*/*z* (EI) 240 (MH^+, 18%), 239 (100), 148 (92) (Found M^+, 239.1308. $C_{16}H_{17}NO$ requires *M*, 239.1310).

Entry 10. Method A was used to give a crude oil that contained none of the desired reduction product **37**, but on purification by column chromatography (30% EtOAc–light petroleum) gave the undesired hydrolysis product (2*S*)-*N*-*tert*-butyl-2-hydroxy-3-phenylpropionamide as a pale yellow oil (25 mg, 0.11 mmol, 52%), $[a]_D^{23}$ −47.6 (*c* 1.72, $CHCl_3$), ν_{max} ($CHCl_3$)/cm^{-1} 3605, 3410, 3065, 3031, 2967, 2931, 2872, 1675, 1603, 1526, 1454, 1410, 1365; δ_H (500 MHz, $CDCl_3$) 1.30 (9H, s, (CH_3)$_3$C), 2.53 (1H, d, *J* 5.1, O*H*), 2.95 (1H, dd, *J* 13.9, 6.4, PhCH_2), 3.13 (1H, dd, *J* 13.9, 6.4, PhCH_2), 4.17 (1H, m, PhCH$_2$C*H*), 6.00 (1H, br s, N*H*), 7.26 (3H, m, Ph*H*), 7.33 (2H, m, Ph*H*); δ_C (126 MHz, $CDCl_3$) 28.7 (CH_3), 41.2 (CH_2), 51.0 (C), 73.0 (CH), 127.1 (CH), 128.9 (CH), 129.7 (CH), 136.9 (C), 171.6 (C=O); *m*/*z* (EI) 205 ($M^+ - O$, 2%), 204 (15), 203 (94), 188 (17) (Found $M^+ - O$, 205.1459. $C_{13}H_{19}NO_2 - O$ requires *M*, 205.1467).

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