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TETRAHEDRON: *ASYMMETRY*

Asymmetric synthesis of α-amino carbonyl derivatives using lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide

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Abstract—An efficient protocol for the transformation of homochiral α-hydroxy-β-amino esters to their α-amino carbonyl components is presented. Diastereoselective conjugate addition of lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide to a range of α,β-unsaturated esters and subsequent enolate hydroxylation with (1*R*)-(−)-(camphorsulfonyl)oxaziridine, followed by $LiAlH_4$ reduction produces homochiral 3-amino-1,2-diols. Subsequent oxidative cleavage with H_5IO_6 provides *N*-benzyl-*N*-α-methylbenzyl protected α-amino aldehydes (96–98% d.e.) and ketones (88% d.e.). Further oxidation of the α-amino aldehydes with sodium chlorite and Pd-catalysed hydrogenation provides α-amino acids in 94–98% e.e.

1. Introduction

The homologation of α-amino acids via the Arndt–Eistert procedure[1] is a routine method for the synthesis of β-amino acids, while the reverse approach to α-amino acids via degradation of homochiral β-amino acids is not yet established. Previous work from our laboratory has shown that the diastereoselective conjugate addition of homochiral lithium amides to α,β-unsaturated esters provides an efficient route for the asymmetric synthesis of homochiral β-amino acid derivatives.[2] Given the ready availability of structurally diverse, homochiral β-amino esters available from application of this chiral lithium amide methodology,[3] we sought a degradative route from β- to α-amino carbonyl derivatives to complement existing methods for α-amino carbonyl syntheses.[4] It was proposed that this transformation could be achieved via the oxidative cleavage of α-hydroxy-β-amino esters **1** (Fig. 1).

The synthesis of the α-hydroxy-β-amino ester structural motif has been the subject of intense investigation,[5] primarily due to its occurrence in the sidechain of the potent anti-cancer agent Taxol[6] and other natural products.[7] We have previously shown that *anti*-α-hydroxy-β-amino acids **4** may be prepared by the conjugate addition of lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide **2** to α,β-unsaturated acceptors and subsequent in situ diastereoselective enolate oxidation with (1*R*)-(−)-(camphorsulfonyl)oxaziridine **3** (Scheme 1).[8]

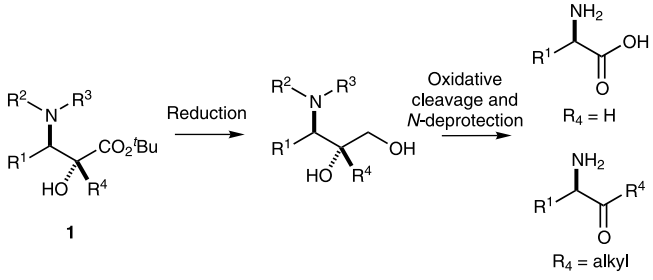

Figure 1.

We report herein how this approach may be utilised as part of an efficient degradation protocol for the asymmetric synthesis of *N*,*N*-protected α-amino aldehydes, ketones and acids all of which have found extensive use as homochiral building blocks in organic synthesis. Part of this work has been communicated previously.[9]

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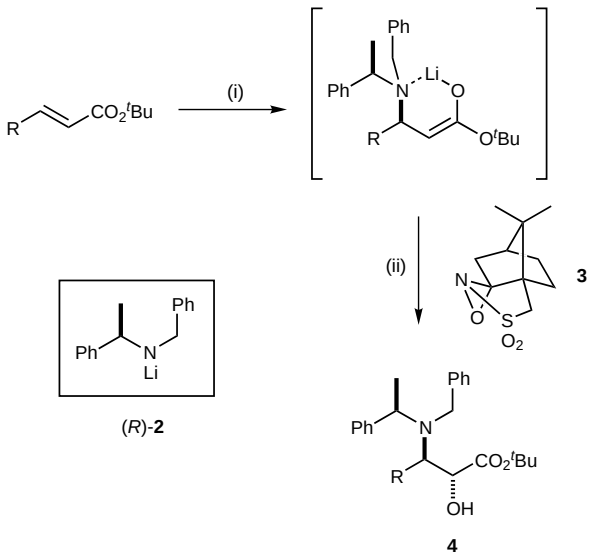


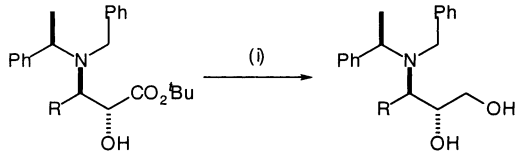
Scheme 1. *Reagents and conditions*: (i) lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide **2** (1.6 equiv.), THF, −78°C, 2 h then (ii) (1*R*)-(−)-(camphorsulfonyl) oxaziridine, THF, −78°C to rt.

2. Results and discussion

2.1. Asymmetric synthesis of α-amino aldehydes

Following our established protocol, conjugate addition of lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide **2** to a range of α,β-unsaturated *tert*-butyl esters **5–9** and subsequent in situ enolate oxidation with (−)-(camphorsulfonyl) oxaziridine gave the *anti*-(2*R*,3*R*)-α-hydroxy-β-amino esters **10–14** with high diastereoselectivity (crude d.e. >88% by ^{1}H NMR spectroscopic analysis). Purification gave the required *anti*-α-hydroxy-β-amino esters esters **10–14** as single diastereoisomers in good to excellent yields. It should be noted that purification to homogeneity at this stage is not strictly necessary as the subsequent degredation protocol can be expected to be equally applicable for the minor *syn*-(2*S*,3*R*)-α-hydroxy-β-amino ester diastereoisomers arising from enolate oxidation (Scheme 2).

Initial attempts to oxidatively decarboxylate α-hydroxy-β-amino esters **10–14** directly were unsatisfactory, therefore degradation of α-hydroxy-β-amino esters **10–14** via the related 1,2-diols was investigated. Thus, $LiAlH_4$ reduction of esters **10–14** afforded the *N*-benzyl-*N*-α-methylbenzyl protected amino diols **15–19** as single diastereoisomers in uniformly excellent yield (90–98%) ready for oxidative cleavage to the *N*-benzyl-*N*-α-methylbenzyl protected aldehydes (Scheme 3).



10-14 15-19

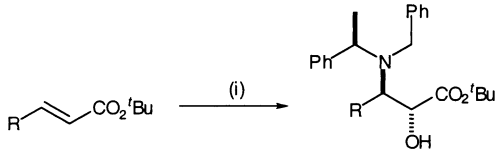
Ester	R	Diol	Yield (%)
10	Me	15	95
11	(*E*)-propenyl	16	90
12	^{t}Bu	17	98
13	Hept	18	92
14	Ph	19	96

Scheme 3. *Reagents and conditions*: (i) $LiAlH_4$, THF, −78°C to rt.

The inherent difficulties associated with the oxidation of primary amino alcohols should not be relevant to tertiary amines[10] and accordingly H_5IO_6 oxidation of amino diols **15–19** proceeded smoothly, furnishing the *N*-benzyl-*N*-α-methylbenzyl protected α-amino aldehydes **20–24** in excellent yield (82–95%) and in high d.e. (96–98%), as determined by ^{1}H NMR spectroscopic analysis. It is noteworthy that only minimal (1–2%) epimerisation is seen upon oxidation to the aldehydes (Scheme 4).

2.2. Asymmetric synthesis of α-amino ketones

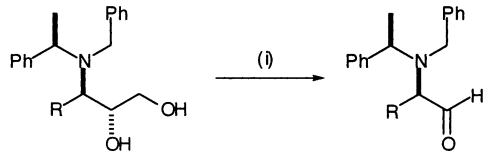
Having demonstrated the utility of this three-step protocol for the asymmetric synthesis of *N*-benzyl-*N*-α-methylbenzyl protected α-amino aldehydes, extension of this methodology to the preparation of both cyclic



5-9 10-14

	R		Yield (%)	crude d.e.
5	Me	10	89	95
6	(*E*)-propenyl	11	89	96
7	^{t}Bu	12	91	>90
8	Hept	13	71	88
9	Ph	14	70	>90

Scheme 2. *Reagents and conditions*: (i) lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide (1.6 equiv.), THF, −78°C, 2 h then (−)-(camphorsulfonyl) oxaziridine, THF, −78°C to rt.



15-19 20-24

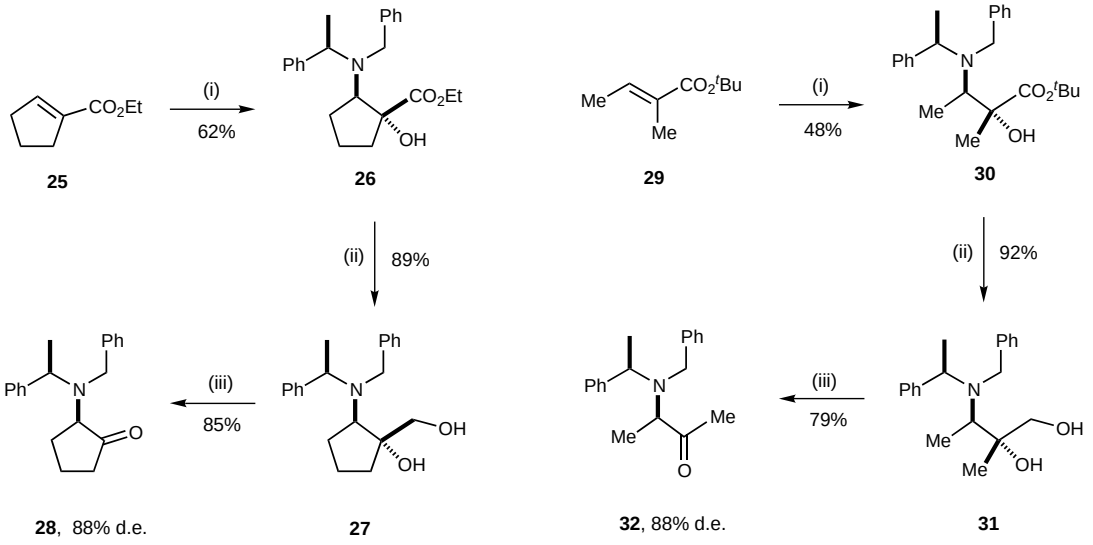
Diol	R	Aldehyde	Yield (%)	d.e. (%)
15	Me	20	95	98
16	(*E*)-propenyl	21	82	96
17	^{t}Bu	22	90	98
18	Hept	23	92	96
19	Ph	24	95	96

Scheme 4. *Reagents and conditions*: (i) H_5IO_6, DCM:H_2O (1:1), 0°C, 30 min.

and acyclic α-amino ketones was investigated. Thus, conjugate addition of lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide to either ethyl 1-cyclopentene-1-carboxylate **25** or *tert*-butyl tiglate **29** followed by subsequent enolate oxidation gave α-hydroxy-β-amino esters **26** and **30**. Conjugate addition/hydroxylation of ethyl 1-cyclopentene-1-carboxylate **25** proceeded with high diastereoselectivity (crude d.e. >90% by ^{1}H NMR analysis), furnishing **26** as a single diastereoisomer in 62% yield after purification. Application of this protocol to *tert*-butyl tiglate **29** generated **30** in only 50% crude d.e.,[11] although purification to homogeneity led to the isolation of **30** as a single diastereoisomer in 48% yield.[12] Subsequent $LiAlH_4$ reduction to the amino diols **27** and **31** (89 and 92% yield, respectively) and oxidative cleavage furnished *N*-benzyl-*N*-α-methylbenzyl protected α-amino ketones **28** and **32** in 85 and 79% yields, respectively. ^{1}H NMR spectroscopic analysis allowed the d.e. of both ketones **28** and **32** to be assessed as 88%, indicating that although the synthesis of *N*-benzyl-*N*-α-methylbenzyl α-amino ketones is facile, slight (6%) epimerisation upon oxidation to the enolisable ketone is observed (Scheme 5).

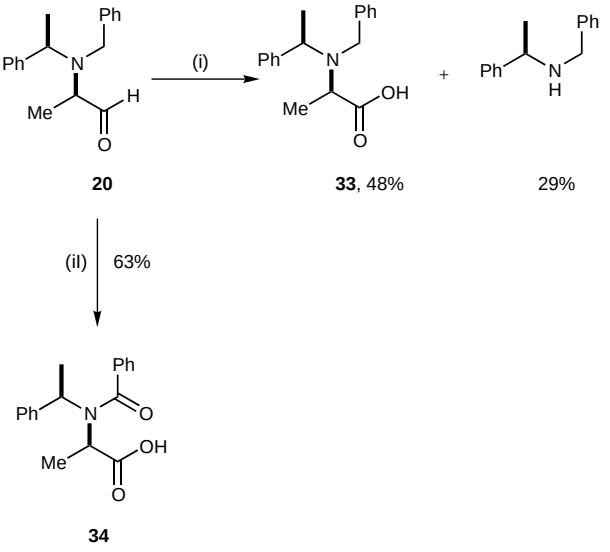
2.3. Asymmetric synthesis of α-amino acids

With routes in hand for the synthesis of *N*-benzyl-*N*-α-methylbenzyl protected α-amino aldehydes and ketones, conversion of α-amino aldehydes **20**–**24** to their α-amino acid hydrochloride salts was investigated. Methods for the chemoselective oxidation of aldehydes to acids in the presence of an amine functionality are comparatively rare,[13] whilst similar oxidations of the corresponding amides are plentiful.[14] Jones' reagent was initially selected as the reagent for this oxidation, with aldehyde **20** used as a model system, in anticipation of in situ protection of the amine from oxidation by protonation under the reaction conditions. Exposure of **20** to Jones' reagent gave rise to the required acid **33** in 48% yield, but with 29% of *N*-benzyl-*N*-α-methylbenzylamine also recovered. Attempted oxidation of aldehyde **20** through $RuCl_3$ catalysed $NaIO_4$ oxidation



Scheme 5. *Reagents and conditions*: (i) lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide (1.6 equiv.), THF, −78°C, 2 h then (−)-(camphorsulfonyl) oxaziridine, THF, −78°C to rt; (ii) $LiAlH_4$, THF, −78°C to rt; (iii) H_5IO_6, DCM:H_2O (1:1), 0°C, 30 min.

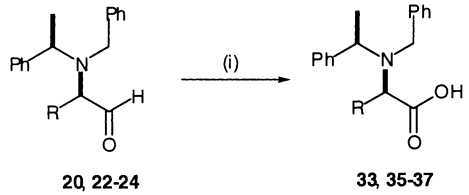
furnished the correct carbonyl oxidation state, but concurrent benzylic oxidation was also noted, furnishing the amide **34** in 63% yield (Scheme 6).[15]



Scheme 6. *Reagents and conditions*: (i) Jones' reagent, acetone 0°C, 2 h; (ii) $NaIO_4$, $RuCl_3$, H_2O–MeCN–CCl_4 (1:3:2), 2 h, rt.

Efficient conversion to the required *N*-benzyl-*N*-α-methylbenzyl amino acid was finally obtained using a protocol involving sodium chlorite oxidation, with cyclohexene as a chlorine trap, which afforded **33** in 54% yield after chromatography. This method was therefore employed for oxidation of aldehydes **22**–**24** to their acid counterparts, giving the *N*-benzyl-*N*-α-methylbenzyl protected acids **35**–**37** in 64–68% yield (Scheme 7).[16]

The *N*-benzyl-*N*-α-methylbenzyl protected α-amino acids **33**, **35**–**37** were subjected to Pd-catalysed hydride transfer deprotection, giving the α-amino acid hydrochloride salts **38**–**41** in excellent yield (91–96%) after treatment with aqueous HCl. The e.e.s of **38**–**41** were unambiguously determined in each case by ^{1}H NMR spectroscopic analysis of the corresponding Mosher's amide derivatives of the derived methyl esters and comparison to authentic racemic samples. Thus, (*R*)-



20, 22-24 33, 35-37

	R		Yield (%)
20	Me	**33**	54
22	^{t}Bu	**35**	64
23	Hept	**36**	68
24	Ph	**37**	64

Scheme 7. *Reagents and conditions*: (i) $NaClO_2$, cyclohexene, MeOH, 0°C.

alanine hydrochloride **38**, (*R*)-leucine hydrochloride **39** and (*R*)-2-amino-nonanoic acid hydrochloride **40** were shown to have been prepared in >98% e.e. and (*R*)-phenylglycine hydrochloride **41** in 94% e.e. (Scheme 8).

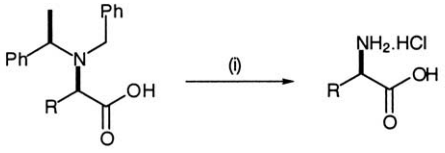
3. Conclusion

In conclusion, this methodology represents a novel asymmetric synthesis of α-amino aldehydes, ketones and acids via the diastereoselective conjugate addition of lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide **2** to α,β-unsaturated esters with concomitant enolate hydroxylation, followed by reduction and oxidative cleavage. Further use of this protocol for the preparation of other α-amino carbonyl derivatives is currently being investigated within our laboratory.

4. Experimental

4.1. General experimental

All reactions involving organometallic or other moisture sensitive reagents were performed under an atmosphere of nitrogen via standard vacuum line techniques. All glassware was flame-dried and allowed to cool under vacuum. In all cases, the reaction diastereoselectivity was assessed by peak integration of the ^{1}H NMR spectrum of the crude reaction mixture. Tetra-



33, 35-37 38-41

	R		Yield (%)	e.e. (%)
33	Me	**38**	92	>98
35	^{t}Bu	**39**	93	>98
36	Hept	**40**	96	>98
37	Ph	**41**	91	94

Scheme 8. *Reagents and conditions*: (i) 4.4% HCO_2H, MeOH, Pd–C, 40°C, 2 h then HCl (aq.).

hydrofuran was distilled under an atmosphere of dry nitrogen from sodium benzophenone ketyl. All other solvents were used as supplied (analytical or HPLC grade), without prior purification. Thin layer chromatography (TLC) was performed on aluminium or plastic sheets coated with 60 F_{254} silica. Sheets were visualised using iodine, UV light or 1% aqueous $KMnO_4$ solution. Flash chromatography was performed on Kieselgel 60 silica. Melting points were recorded on a Gallenkamp hot stage apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker DPX 400 (^{1}H: 400 MHz and ^{13}C: 100.6 MHz) or Bruker AMX 500 (^{1}H: 500 MHz and ^{13}C: 125 MHz) spectrometer in the deuterated solvent stated. All chemical shifts (δ) are quoted in ppm and coupling constants (J) in Hz. Coupling constants are quoted twice, each being recorded as observed in the spectrum without averaging. Residual signals from the solvents were used as an internal reference. ^{13}C multiplicities were assigned using a DEPT sequence. Infrared spectra were recorded on a Perkin–Elmer 1750 IR Fourier Transform spectrophotometer using either thin films on NaCl plates (film) or KBr discs (KBr) as stated. Only the characteristic peaks are quoted in cm^{-1}. High resolution mass spectra (HRMS) wee recorded on a Micromass Autospec 500 OAT spectrometer or on a Waters 2790 Micromass LCT Exact Mass Electrospray Ionisation Mass Spectrometer. Techniques used were chemical ionisation (CI, NH_3) or atmospheric pressure chemical ionisation (APCI). Optical rotations were recorded on a Perkin–Elmer 241 polarimeter with a path length of 1 dm. Concentrations are quoted in g/100 ml.

4.2. General procedure 1: conjugate addition/ hydroxylation

n-BuLi (1.6 equiv.) was added to a solution of the amine (2.0 equiv.) in THF at −78°C. After 30 min the requisite α,β-unsaturated acceptor (1.0 equiv.) in THF was added by cannula. After 2 h, (1*R*)-(−)-(10-camphorsulfonyl)oxaziridine (2.0 equiv.) was added and the reaction was stirred for 15 min at −78°C before warming to rt. After 12 h, saturated ammonium chloride solution (1–2 ml) was added before concentration in vacuo and the residue was extracted with Et_2O. The organic extracts were washed sequentially with 10% citric acid solution (20 ml), saturated sodium bicarbonate (20 ml) and brine (20 ml) before concentration in vacuo to afford the crude product.

4.3. General procedure 2: $LiAlH_4$ reduction of *tert*-butyl esters to alcohols

$LiAlH_4$ (1.0 equiv., 1.0 M in THF) was added dropwise to a solution of the β-amino ester (1.0 equiv.) THF (5–20 ml) at −78°C before warming to rt. The reaction was stirred for 24 h before cautious addition of 2 M NaOH, then heated at reflux for 30 min before being filtered through Celite®, washed with Et_2O (2×20 ml) and concentrated in vacuo to yield the crude product.

4.4. General procedure 3: oxidation of 1,2 diols with H_5IO_6

H_5IO_6 (1.1 equiv.) in H_2O (1–5 ml) was added to a stirred solution of the amino diol (1.0 equiv.) in DCM (1–5 ml) at 0°C and stirred vigorously for 30 min before extraction with Et_2O (2×20 ml). The organic extracts were washed with saturated sodium bicarbonate (20 ml) and brine (20 ml) before concentration in vacuo to afford the crude product.

4.5. General procedure 4: oxidation of aldehydes to acids with $NaClO_2$

Cyclohexene (1.0 ml) followed by $NaClO_2$ (1.1 equiv.) was added to the aldehyde (1.0 equiv.) in MeOH (1–5 ml) at 0°C and stirred for 4 h before extraction with Et_2O (2×20 ml). The organic extracts were washed with saturated sodium bicarbonate (20 ml) and brine (20 ml) before concentration in vacuo to afford the crude product.

4.6. General procedure 5: Pd-catalysed debenzylation

The *N*-benzyl-*N*-α-methylbenzyl amino acid was dissolved in a solution of 4.4% formic acid in MeOH (10 ml) before the addition of Pd–C (10 mol%) and heated at 40°C for 2 h. Upon cooling, the suspension was filtered through a plug of Celite®, acidified (1 ml, 10 M HCl) and concentrated in vacuo to afford the title compound.

4.7. Preparation of (2*R*,3*R*,α*R*)-*tert*-butyl 2-hydroxy-3-(*N*-benzyl-*N*-α-methylbenzylamino)butanoate 10[8]

Following general procedure 1, *tert*-butyl crotonate[17] **5** (2.84 g, 20 mmol) in THF (40 ml), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (6.8 g, 32 mmol) in THF (50 ml), *n*-BuLi (2.5 M, 12.4 ml, 31 mmol) and (1*R*)-(−)-(10-camphorsulfonyl)oxaziridine (9.2 g, 40 mmol) gave, after chromatographic purification on silica (hexane–ether, 10:1–5:1), **10** as a white solid (6.55 g, 89%); $[\alpha]_D^{25} = -33.4$ (*c* 1.0, $CHCl_3$) {lit.[8] $[\alpha]_D^{22} = -35.2$ (*c* 1.0, $CHCl_3$)}; mp 88°C (lit.[8] 88–89°C); δ_H (500 MHz, $CDCl_3$) 7.47–7.18 (10H, m, *Ph*), 4.02 (1H, q, $J_{6.8}$, C(α)*H*), 3.99 (1H, d, $J_{2,3}$ 10.0, C(2)*H*), 3.98 (1H, AB, $J_{14.9}$, NCH_B), 3.88 (1H, AB, $J_{14.9}$, NCH_A), 3.26 (1H, dq, $J_{3,2}$ 10.0, $J_{3,4}$ 7.0, C(3)*H*), 2.88 (1H, br s, O*H*), 1.36 (9H, s, OCMe_3), 1.32 (3H, d, $J_{6.8}$, C(α)*Me*), 1.07 (3H, d, $J_{7.0}$, C(4)H_3).

4.8. Preparation of (4*E*,2*R*,3*R*,α*R*)-*tert*-butyl 2-hydroxy-3-(*N*-benzyl-*N*-α-methylbenzylamino)hex-4-enoate 11

Following general procedure 1, *tert*-butyl sorbate[18] **6** (1.68 g, 10 mmol) in THF (20 ml), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (3.4 g, 16 mmol) in THF (25 ml), and *n*-BuLi (2.5 M, 6.2 ml, 15.5 mmol) and (1*R*)-(−)-(10-camphorsulfonyl)oxaziridine (4.6 g, 20 mmol) gave, after chromatographic purification on silica (hexane–ether, 10:1–5:1), **11** as a colourless oil (3.54 g, 89%); $[\alpha]_D^{25} = -64.8$ (*c* 1.0, $CHCl_3$); ν_{max} (film) 3503 (O-H),

2977 (C-H), 1725 (C=O); δ_H (500 MHz, $CDCl_3$) 7.42–7.17 (10H, m, *Ph*), 5.69 (1H, m, C(4)*H*), 5.52 (1H, dq, $J_{5,4}$ 15.3, $J_{5,6}$ 6.4, C(5)*H*), 4.24 (1H, q, $J_{6.8}$, C(α)*H*), 4.09 (1H, d, $J_{2,3}$ 2.6, C(2)*H*), 3.98 (1H, AB, $J_{14.5}$, NCH_B), 3.79 88 (1H, AB, $J_{14.5}$, NCH_A), 3.56 (1H, dd, $J_{3,4}$ 9.7, $J_{3,2}$ 2.6, C(3)*H*), 2.87 (1H, br s, O*H*), 1.70 (3H, dd, $J_{6,5}$ 6.4, $J_{6,4}$ 1.3, C(6)H_3), 1.36 (3H, d, *J* 6.8, C(α)*Me*), 1.33 (9H, s, OCMe_3); δ_C (100 MHz, $CDCl_3$) 172.7 (*C*=O), 144.2, 141.6 (Ph_{ipso}) 129.7, 128.4, 128.2, 128.0, 127.9 ($Ph_{o-,m-,p-}$), 126.7, 126.6 (C(4)=C(5)), 81.8 (*C*Me$_3$, 74.4 (*C*(*2*)H), 63.2 (*C*(α)H), 56.8 (*C*(*3*)H), 51.5 (N*C*H$_2$), 27.9 (C*Me*$_3$), 18.1 (C(6)*Me*), 14.8 (C(α)*Me*); HRMS (CI$^+$) $C_{25}H_{34}NO_3$ requires 396.2539; found 396.2532.

4.9. Preparation of (2*R*,3*R*,α*R*)-*tert*-butyl 2-hydroxy-3-(*N*-benzyl-*N*-α-methylbenzylamino)-5-methylhexanoate 12

Following general procedure 1, (*E*)-*tert*-butyl 5-methyl-hex-2-enoate[19] **7** (1.84 g, 10 mmol) in THF (20 ml), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (3.4 g, 16 mmol) in THF (25 ml), *n*-BuLi (2.5 M, 6.2 ml, 15.5 mmol) and (1*R*)-(−)-(10-camphorsulfonyl)oxaziridine (4.6 g, 20 mmol) gave, after chromatographic purification on silica (hexane–ether, 10:1–5:1), **12** as a colourless oil (3.74 g, 91%); $[\alpha]_D^{22} = -18.9$ (*c* 1.0, $CHCl_3$); ν_{max} (film) 1722 (C=O); δ_H (500 MHz, $CDCl_3$) 7.48–7.22 (10H, m, *Ph*), 4.35 (1H, AB, *J* 15.6, NCH_B), 3.99 (1H, d, $J_{2,3}$ 1.4, C(2)*H*), 3.95 (1H, q, *J* 7.0, C(α)*H*), 3.66 (1H, AB, *J* 15.6, NCH_A), 3.26 (1H, m, C(3)*H*), 2.89 (1H, br d, *J* 1.9, O*H*), 1.94, (1H, m, C(5)*H*), 1.59 (2H, m, C(4)H_2), 1.45 (9H, s, OCMe_3), 1.29 (3H, d, *J* 7.0, C(α)*Me*), 0.90 (3H, d, *J* 6.8, C(5)CH_3), 0.68 (3H, d, *J* 6.5, C(5)CH_3); δ_C (50 MHz, $CDCl_3$) 174.9 (*C*=O), 144.1, 143.5 (Ph_{ipso}) 128.4, 128.2, 127.9, 127.2, 126.5 ($Ph_{o-,m-,p-}$), 82.5 (*C*Me$_3$, 71.1 (*C*(*2*)H), 59.4 (*C*(α)H), 57.0 (*C*(*3*)H), 51.0 (N*C*H$_2$), 36.9 (*C*(*4*)H$_2$), 28.0 (C*Me*$_3$), 24.1 (*C*(*5*)H), 23.6, 22.1 (C(5)(*C*H$_3$)$_2$), 20.4 (C(α)*Me*); HRMS (CI$^+$) $C_{26}H_{38}NO_3$ requires 412.2852; found 412.2856.

4.10. Preparation of (2*R*,3*R*,α*R*)-*tert*-butyl 2-hydroxy-3-(*N*-benzyl-*N*-α-methylbenzylamino)decanoate 13

Following general procedure 1, (*E*)-*tert*-butyl dec-2-enoate[19] **8** (2.3 g, 10 mmol) in THF (20 ml), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (3.4 g, 16.0 mmol) in THF (25 ml), *n*-BuLi (2.5 M, 6.2 ml, 15.5 mmol) and (1*R*)-(−)-(10-camphorsulfonyl)oxaziridine (4.6 g, 20 mmol) gave, after chromatographic purification on silica (hexane–ether, 10:1–5:1), **13** as a colourless oil (3.2 g, 71%); $[\alpha]_D^{22}$ −23.2 (*c* 1.0, $CHCl_3$); {lit.,[20] $[\alpha]_D^{22} = -24.6$ (*c* 1.02, $CHCl_3$)}; δ_H (500 MHz, $CDCl_3$) 7.48–7.18 (10H, m, *Ph*), 4.26 (1H, AB, *J* 15.4, NCH_B), 3.99–3.92 (2H, m, C(2)*H* and C(α)*H*), 3.69 (1H, AB, *J* 15.6, NCH_A), 3.23–3.19 (1H, m, C(3)*H*), 2.89 (1H, d, *J* 6.0, O*H*), 1.69–1.10 (12H, m, $CH_3(CH_2)_6$), 1.45 (9H, s, OCMe_3), 1.29 (3H, d, *J* 7.0, C(α)*Me*), 0.90 (3H, d, *J* 6.8, C(10)H_3), identical to that previously prepared in the literature.[20]

4.11. Preparation of (2*R*,3*R*,α*R*)-*tert*-butyl 2-hydroxy-3-phenyl-3-(*N*-benzyl-*N*-α-methylbenzylamino)propanoate 14[8]

Following general procedure 1, *tert*-butyl cinnamate **9** (4.1 g, 20 mmol) in THF (40 ml), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (6.8 g, 32 mmol) in THF (50 ml), *n*-BuLi (2.5 M, 12.4 ml, 31 mmol) and (1*R*)-(−)-(10-camphorsulfonyl)oxaziridine (9.2 g, 40 mmol), gave, after chromatographic purification on silica (hexane–ether, 10:1–5:1), **14** as a white solid (6.00 g, 70%); $[\alpha]_D^{25} = -23.4$ (*c* 1.0, $CHCl_3$), {lit.[8] $[\alpha]_D^{20} = -27.2$ (*c* 1.0 $CHCl_3$)}; mp 87°C (lit.[8] mp 87–88°C); δ_H (500 MHz, $CDCl_3$) 7.49–7.17 (15H, m, *Ph*), 4.40 (1H, br s, C(2)*H*), 4.22 (1H, q, *J* 6.9, C(α)*H*), 4.22 (1H, d, $J_{3,2}$ 3.2, C(3)*H*), 4.14 (1H, AB, *J* 15.0, NCH_B), 3.83 (1H, AB, *J* 15.0, NCH_A), 2.77 (1H, d, *J* 3.7, O*H*), 1.21 (3H, d, *J* 6.9, C(α)*Me*), 1.20 (9H, s, OCMe_3).

4.12. Preparation of (2*R*,3*R*,α*R*)-2-hydroxy-3-(*N*-benzyl-*N*-α-methylbenzylamino)butanol 15

Following general procedure 2, **10** (600 mg, 1.5 mmol) and $LiAlH_4$ (1.5 mmol) in THF (3 ml) gave, after chromatographic purification (Et_2O), **15** (427 mg, 95%) as a colourless oil; $[\alpha]_D^{25} = -22.8$ (*c* 1.0, $CHCl_3$); ν_{max} (film) 3391 (OH); δ_H (500 MHz, $CDCl_3$) 7.40–7.23 (10H, m, *Ph*), 3.96 (1H, q, *J* 6.9, C(α)*H*), 3.82 (1H, AB, *J* 13.6, NCH_B), 3.74 (1H, AB, *J* 13.6, NCH_A), 3.39 (3H, m, C(2)*H*(OH)C(1)H_2), 2.87 (1H, m, C(3)*H*), 1.43 (3H, d, *J* 6.9, C(α)*Me*), 1.27 (3H, d, *J* 6.9, C(4)H_3); δ_C (125 MHz, $CDCl_3$) 143.6, 140.3 (Ph_{ipso}), 129.0, 128.5, 128.2, 128.1, 127.2, 127.1 ($Ph_{o-,m-,p-}$), 73.9 (*C*(2)H), 64.4 (C(1)H_2OH), 56.4 (C(α)H), 52.3 (*C*(3)H), 51.1 (N*C*H$_2$), 13.9 (C(α)*Me*), 12.8 (*C*(4)H$_3$); HRMS (CI$^+$) $C_{19}H_{26}NO_2$ requires 300.1964; found 300.1978.

4.13. Preparation of (4*E*,2*R*,3*R*,α*R*)-2-hydroxy-3-(*N*-benzyl-*N*-α-methylbenzylamino)hex-4-enol 16

Following general procedure 2, **11** (800 mg, 2.0 mmol) and $LiAlH_4$ (2.0 mmol) in THF (5 ml) gave, after chromatographic purification (Et_2O), **16** (593 mg, 90%) as a colourless oil; $[\alpha]_D^{22} = -48.7$ (*c* 1.0, $CHCl_3$); ν_{max} (film) 3393 (OH); δ_H (500 MHz, $CDCl_3$) 7.36–7.24 (10H, m *Ph*), 5.72 (2H, m, C(4)*H*=C(5)*H*), 4.07 (1H, q, *J* 6.9, C(α)*H*), 3.90 (1H, AB, *J* 13.7, NCH_B), 3.68 (1H, AB, *J* 13.7, NCH_A), 3.60 (1H, ddd, *J* 9.9, *J* 5.4, *J* 4.5, C(2)*H*), 3.44 (2H, m, C(1)H_2OH), 3.17 (1H, ddd, *J* 8.1, *J* 5.4, *J* 2.7, C(3)*H*), 1.83 (3H, d, *J* 4.8, C(6)H_3), 1.41 (3H, d, *J* 6.9, C(α)*Me*); δ_C (125 MHz, $CDCl_3$) 143.6, 140.3 (Ph_{ipso}), 131.5 (*C*(4)H), 128.8, 128.5, 128.4, 128.2, 128.1, 127.2, 127.1 (*C*(5)H, $Ph_{o-,m-,p-}$), 71.3 (*C*(2)H), 64.9 (*C*(1)H$_2$) 62.6 (*C*(3)H), 55.5 (*C*(α)H), 51.6 (N*C*H$_2$), 18.3 (*C*(6)H$_3$) 13.5 (C(α)*Me*); HRMS (CI$^+$) $C_{21}H_{28}NO_2$ requires 326.2120; found 326.2128.

4.14. Preparation of (2*R*,3*R*,α*R*)-2-hydroxy-3-(*N*-benzyl-*N*-α-methylbenzylamino)-5-methylhexanol 17

Following general procedure 2, **12** (2.23 g, 5.4 mmol) and $LiAlH_4$ (5.4 ml) in THF (10 ml) gave, after chro-

matographic purification (Et_2O), **17** (1.81 g, 98%) as a colourless oil; $[\alpha]_D^{25} = -21.0$ (*c* 1.0, $CHCl_3$); ν_{max} (film) 3401 (OH); δ_H (500 MHz, $CDCl_3$) 7.47–7.26 (10H, m, *Ph*), 4.06 (1H, AB, *J* 14.6, NCH_B), 3.97 (1H, q, *J* 6.9, C(α)*H*), 3.80 (1H, AB, *J* 14.6, NCH_A), 3.57 (1H, m, C(2)*H*), 3.41 (2H, m, C(1)H_2), 2.90 (1H, m, C(3)*H*), 2.75 (2H, br s, CH(O*H*)CH_2O*H*), 1.90 (1H, m, (C(5)*H*), 1.59 (1H, m, (C(4)H_A), 1.39 (3H, d, *J* 6.9, C(α)*Me*), 1.36 (1H, obscured, (C(4)H_B), 1.02 (3H, d, *J* 6.6, C(5)CH_3), 0.87 (3H, d, *J* 6.5, C(5)CH_3); δ_C (125 MHz, $CDCl_3$) 144.0, 141.7 (Ph_{ipso}), 128.5, 127.9, 127.2, 126.9 ($Ph_{o-,m-,p-}$), 72.0 (*C*(*2*)H), 64.5 (*C*(*1*)H_2), 58.1 (*C*(α)H), 54.9 (*C*(*3*)H), 51.7 (N*C*H_2) 37.9 (*C*(*4*)H_2), 25.2 (*C*(*5*)H), 23.3, 22.9 (C(5)(*C*H_3)$_2$), 16.3 (C(α)*Me*); HRMS (CI^+) $C_{22}H_{32}NO_2$ requires 342.2433; found 342.2436.

4.15. Preparation of (2*R*,3*R*,α*R*)-2-hydroxy-3-(*N*-benzyl-*N*-α-methylbenzyl)aminodecanol 18

Following general procedure 2, **13** (45 mg, 0.1 mmol) and $LiAlH_4$ (0.1 ml) in THF (2 ml) gave, after chromatographic purification (Et_2O), **18** (35 g, 92%) as a colourless oil; $[\alpha]_D^{25} = -37.6$ (*c* 1.1, $CHCl_3$); ν_{max} (film) 3368 (OH); δ_H (500 MHz, $CDCl_3$) 7.42–7.22 (10H, m, *Ph*), 3.93 (1H, q, *J* 6.9, C(α)*H*), 3.89 (1H, AB, *J* 14.2, NCH_B), 3.77 (1H, AB, *J* 14.2, NCH_A), 3.47 (3H, m, C(2)*H*(OH)C(1)H_2), 2.77 (1H, dt, *J* 7.7, *J* 4.5, C(3)*H*), 1.71 (1H, m, C(4)H_A), 1.51 (1H, m, C(4)H_B), 1.39 (3H, d, *J* 6.9, C(α)*Me*), 1.37–1.27 (10H, m, CH_3(CH_2)$_5$), 0.92 (3H, t, *J* 6.9, C(10)H_3); δ_C (125 MHz, $CDCl_3$) 143.7, 140.7 (Ph_{ipso}), 128.7, 128.5, 128.4, 127.9, 127.2, 127.1 ($Ph_{o-,m-,p-}$), 72.6 (*C*(*2*)H), 64.1 (*C*(*1*)H_2), 51.8 {*C*(α)H), (*C*(*3*)H)}, 51.8 (N*C*H_2), 31.9, 30.1, 29.2, 28.8, 28.1, 22.7, (CH_3(CH_2)$_6$), 14.1 (C(α)*Me*), 13.9 (*C*(10)H_3); HRMS (CI^+) $C_{25}H_{38}NO_2$ requires 384.2903; found 384.2900.

4.16. Preparation of (2*R*,3*R*,α*R*)-2-hydroxy-3-(*N*-benzyl-*N*-α-methylbenzylamino)-4-phenylbutanol 19

Following general procedure 2, **14** (2.0 g, 4.64 mmol) and $LiAlH_4$ (4.6 ml) in THF (10 ml) gave, after chromatographic purification (Et_2O), **19** (1.61 g, 96%) as a colourless oil; $[\alpha]_D^{22}$ −48.0 (*c* 0.5, $CHCl_3$); ν_{max} (film) 3400 (OH); δ_H (500 MHz, $CDCl_3$) 7.47–7.25 (15H, m, *Ph*), 4.16 (1H, ddd, *J* 7.3, *J* 6.6, *J* 3.7, C(2)*H*(OH)), 4.21 (1H, q, *J* 6.9, C(α)*H*), 4.02 (1H, AB, *J* 14.1, NCH_B), 3.77 (1H, d, *J* 7.5, C(3)*H*), 3.61 (1H, dd, $J_{1A,1B}$ 11.2, $J_{1A,2}$ 3.7, C(1)H_A), 3.57 (1H, AB, *J* 14.1, NCH_A), 3.34 (1H, dd, $J_{1B,1A}$ 11.2, $J_{1B,2}$ 6.5, C(1)H_B), 1.84, 1.65 (2H, br s, CH(O*H*)CH_2O*H*), 1.08 (3H, d, *J* 6.9, C(α)*Me*); δ_C (125 MHz, $CDCl_3$) 143.9, 140.6, 138.1 (Ph_{ipso}), 129.7, 128.7, 128.5, 128.3, 128.0, 127.8, 127.2, 127.0 ($Ph_{o-,m-,p-}$), 71.0 (*C*(*2*)H), 65.5 (*C*(*3*)H), 64.9 (*C*(*1*)H_2), 56.1 (*C*(α)H), 51.5 (N*C*H_2), 12.2 (C(α)*Me*); HRMS (CI^+) $C_{24}H_{28}NO_2$ requires 362.2120; found 362.2122.

4.17. Preparation of (2*R*,α*R*)-2-(*N*-benzyl-*N*-α-methylbenzylamino)propanal 20

Following general procedure 3, **15** (56 mg, 0.19 mmol) and H_5IO_6 (47 mg, 0.21 mmol) gave **20** (48 g, 95%) as a colourless oil; $[\alpha]_D^{22} = +1.2$ (*c* 1.0, $CHCl_3$); ν_{max} (film) 1728 (C=O); δ_H (500 MHz, $CDCl_3$) 9.41 (1H, s, CHC*H*O), 7.46–7.25 (10H, m, *Ph*), 4.05 (1H, q, *J* 6.8, C(α)*H*), 3.81 (1H, AB, *J* 14.0, NCH_B), 3.76 (1H, AB, *J* 14.0, NCH_A), 3.38 (1H, q, *J* 6.9, C(2)*H*), 1.46 (3H, d, *J* 6.8, C(α)*Me*), 1.23 (3H, d, *J* 6.9, C(3)H_3); δ_C (125 MHz, $CDCl_3$) 203.7 (*C*=O), 144.0, 140.0 (Ph_{ipso}), 128.9, 128.3, 127.7, 127.3, 127.2 ($Ph_{o-,m-,p-}$), 61.5 (*C*(2)H), 58.1 (*C*(α)H), 51.6 (N*C*H_2), 17.1 (C(α)*Me*), 13.3 (*C*(3)); HRMS (CI^+) $C_{18}H_{22}NO$ requires 268.1701; found 268.1701.

4.18. Preparation of (3*E*,2*R*,α*R*)-2-(*N*-benzyl-*N*-α-methylbenzylamino)pent-3-enal 21

Following general procedure 3, **16** (600 mg, 1.85 mmol) and H_5IO_6 (463 mg, 2.0 mmol) gave **21** (441 mg, 82%) as a colourless oil; $[\alpha]_D^{24} = +14.6$ (*c* 1.0, $CHCl_3$); ν_{max} (film) 1727 (C=O); δ_H (500 MHz, $CDCl_3$) 9.32 (1H, d, *J* 1.2, C*H*O), 7.49–7.20 (10H, m *Ph*), 5.70 (1H, dq, $J_{4,3}$ 15.5, $J_{4,5}$ 6.2, C(4)*H*), 5.62 (1H, dd, $J_{3,4}$ 15.5, $J_{3,2}$ 8.1, C(3)*H*), 4.08 (1H, q, *J* 6.8, C(α)*H*), 3.85 (1H, AB, *J* 14.1, NCH_B), 3.77 (1H, d, *J* 8.0, C(2)*H*), 3.73 (1H, AB, *J* 14.1, NCH_A), 1.80 (3H, dd, $J_{5,4}$ 6.2, $J_{5,3}$ 1.0, C(5)H_3), 1.44 (3H, d, *J* 6.8, C(α)*Me*), δ_C (125 MHz, $CDCl_3$) 201.3 (*C*=O), 143.6, 139.9 (Ph_{ipso}), 132.7 (*C*(4)H), 129.3, 129.1, 128.8, 128.6, 128.3, 128.2, 127.8, 127.5 ($Ph_{o-,m-,p-}$), 124.4 (*C*(5)H), 70.5 (*C*(2)H), 57.5 (*C*(α)H), 51.9 (N*C*H_2), 18.4 (*C*(5)H_3), 16.0 (C(α)*Me*); HRMS (CI^+) $C_{20}H_{24}NO$ requires 294.1858; found 294.1859.

4.19. Preparation of (2*R*,α*R*)-2-(*N*-benzyl-*N*-α-methylbenzylamino)-4-methylpentanal 22

Following general procedure 3, **17** (363 mg, 1.07 mmol) and H_5IO_6 (267 mg, 1.17 mmol) gave **22** (295mg, 90%) as a colourless oil; $[\alpha]_D^{22} = +1.3$ (*c* 0.63, $CHCl_3$); ν_{max} (film)/cm^{-1} 1723 (C=O); δ_H (500 MHz, $CDCl_3$) 9.42 (1H, s, C*H*O), 7.51–7.27 (10H, m, *Ph*), 4.16 (1H, q, *J* 6.8, C(α)*H*), 4.00 (1H, AB, *J* 14.7, NCH_B), 3.96 (1H, AB, *J* 14.7, NCH_A), 3.41 (1H, t, *J* 6.4, C(2)*H*), 1.82 (1H, app sept, *J* 6.6, C(4)*H*), 1.77 (1H, m, C(3)H_2), 1.51 (3H, d, *J* 6.9, C(α)*Me*), 1.50 (1H, obscured, C(3)H_A), 0.95 (3H, d, *J* 6.8, C(4)CH_3), 0.93 (3H, d, *J* 6.8, C(4)CH_3); δ_C (125 MHz, $CDCl_3$) 203.9 (*C*=O), 144.2, 141.3 (Ph_{ipso}), 128.9, 128.8, 128.3, 127.8, 127.5 ($Ph_{o-,m-,p-}$), 64.2 (*C*(α)H), 58.9 (*C*(*2*)H), 51.1 (N*C*H_2), 36.1 *C*(*3*)H_2), 25.7 (*C*(*4*)H) 23.3, 23.2 (C(4)(*C*H_3)$_2$), 18.7 (C(α)*Me*); HRMS (CI^+) $C_{21}H_{28}NO$ requires 310.2171; found 310.2177.

4.20. Preparation of (2*R*,α*R*)-2-(*N*-benzyl-*N*-α-methylbenzylamino)nonanal 23

Following general procedure 3, **18** (260 mg, 0.68 mmol) and H_5IO_6 (170 mg, 0.75 mmol) gave **23** (220 mg, 92%) as a colourless oil; $[\alpha]_D^{22} = +1.1$ (*c* 0.75, $CHCl_3$); ν_{max} (film) 1728 (C=O); δ_H (500 MHz, $CDCl_3$) 9.30 (1H, s, C*H*O), 7.40–7.25 (10H, m, *Ph*), 4.06 (1H, q, *J* 6.9, C(α)*H*), 3.87 (2H, AB m, NCH_2), 3.24 (1H, t, *J* 6.6, C(2)*H*), 1.78 (1H, m, C(3)*H*), 1.54 (1H, m, C(3)*H*), 1.42 (3H, d, *J* 6.9, C(α)*Me*), 1.40–1.27 (10H, m, (CH_2)$_5$), 0.90 (3H, t, *J* 6.8, C(9)H_3); δ_C (125 MHz, $CDCl_3$) 203.3 (*C*=O), 143.7, 140.6 (Ph_{ipso}), 128.5, 128.4, 128.3, 127.7, 127.3, 127.0 ($Ph_{o-,m-,p-}$), 65.9 (*C*(α)H), 58.3 (*C*(*2*)H), 51.6 (N*C*H_2), 31.8, 29.7, 29.1, 27.1, 26.6, 22.6 ((*C*H_2)$_6$) 18.2 (C(α)*Me*), 14.1 (*C*(*9*)H_3); HRMS (CI^+) $C_{24}H_{34}NO$ requires 352.2640; found 352.2620.

4.21. Preparation of (2*R*,α*R*)-2-phenyl-2-(*N*-benzyl-*N*-α-methylbenzylamino)ethanal 24

Following general procedure 3, **19** (255 mg, 0.71 mmol) and H_5IO_6 (229 mg, 1.00 mmol) gave **24** (221 mg, 95%) as a colourless oil; $[\alpha]_D^{22} = +1.1$ (*c* 0.75, $CHCl_3$); ν_{max} (film) 1727 (C=O); δ_H (500 MHz, $CDCl_3$) 9.13 (1H, d, *J* 3.8, C*H*O), 7.52–7.14 (15H, m *Ph*), 4.40 (1H, d, *J* 3.7, C(2)*H*), 4.12 (1H, q, *J* 6.8, C(α)*H*), 3.92 (1H, AB, *J* 14.4, NCH_B), 3.58 (1H, AB, *J* 14.4, NCH_A), 1.34 (3H, d, *J* 6.8, C(α)*Me*); δ_C (50 MHz, $CDCl_3$) 199.2 (*C*=O), 143.3, 140.0, 135.4 (*Ph*$_{ipso}$), 129.4, 129.2, 129.0, 128.6, 128.3, 128.2, 127.2 (*Ph*$_{o\text{-},m\text{-},p\text{-}}$), 76.5 (*C*(2)H), 56.3 (*C*(α)H), 52.4 (N*C*H$_2$), 12.0 (C(α)*Me*); *m*/*z* (APCI$^+$) 330 (MH$^+$, 70%), 226 (MH$^+$ −PhCHCH$_3$).

4.22. Preparation of (1*R*,2*R*,α*R*)-ethyl 1-hydroxy-2-(*N*-benzyl-*N*-α-methylbenzylamino)cyclopentanecarboxylate 26

Following general procedure 1, ethyl cyclopent-1-enecarboxylate[21] **25** (1.40 g, 10.5 mmol) in THF (20 ml), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (3.6 g, 16.8 mmol) in THF (20 ml), *n*-BuLi (2.5 M, 6.5 ml, 16.3 mmol) and (1*R*)-(−)-(10-camphorsulfonyl)oxaziridine (4.8 g, 21 mmol), gave, after chromatographic purification (hexane:Et_2O, 10:1–5:1), **26** (2.34 g, 62%) as a colourless oil; $C_{23}H_{29}NO_3$ requires C, 75.2; H, 7.95; N, 3.8; found C, 75.5; H, 7.9; N, 3.95%; $[\alpha]_D^{25} = +11.0$ (*c* 1.0, $CHCl_3$); ν_{max} (film) 1714 (C=O); δ_H (500 MHz, $CDCl_3$) 7.35–7.13 (10H, m, *Ph*), 4.17 and 4.00 (2×1H, dq, *J* 7.0, *J* 3.5, $CO_2CH_2CH_3$), 3.84 (1H, q, *J* 6.6, C(α)*H*), 3.73 (1H, AB, *J* 14.0, NCH_B), 3.60 (1H, AB, *J* 14.0, NCH_A), 3.10 (1H, dd, *J* 12.0, *J* 7.3, C(2)*H*), 2.34 (1H, s, O*H*), 2.33–1.52 (6H, m, CH(CH_2)$_3$), 1.21 (3H, d, *J* 6.6, C(α)*Me*), 1.14 (3H, t, *J* 7.1, OCH_2CH_3); δ_C (125 MHz, $CDCl_3$) 175.9 (C=O), 143.9, 140.7 (Ph$_{ipso}$), 128.6, 128.3, 128.2, 128.1, 126.9, 126.8 (Ph$_{o\text{-},m\text{-},p\text{-}}$), 83.8 (*C*(1)), 70.8 (*C*(α)H), 61.4 ($CO_2CH_2CH_3$), 55.4 (*C*(2)H), 52.0 (N*C*H$_2$), 35.3, 28.2, 21.5 ((*C*H$_2$)$_3$), 13.9 (*C*(α)Me), 11.3 ($CO_2CH_2CH_3$); HRMS (CI$^+$) $C_{23}H_{29}NO_3$ requires 368.2230; found 368.2226.

4.23. Preparation of (1*R*,2*R*,α*R*)-1-hydroxymethyl-2-(*N*-benzyl-*N*-α-methylbenzylamino)cyclopentanol 27

Following general procedure 2, **26** (1.10 g, 3.05 mmol) and $LiAlH_4$ (3.1 ml) in THF (8 ml) gave, after chromatographic purification (Et_2O), **27** (864 mg, 89%) as a colourless oil; $[\alpha]_D^{25} = -69.0$ (*c* 1.0, $CHCl_3$); ν_{max} (film) 3418 (OH); δ_H (500 MHz, $CDCl_3$) 7.51–7.23 (10H, m, *Ph*), 4.26 (1H, br d, *J* 9.6, C(OH)CH$_2$O*H*), 3.98 (1H, q, *J* 6.9, C(α)*H*), 3.89 (1H, d, *J* 10.5, C(1′)H_A), 3.79 (2H, app s, NCH_2), 3.40 (1H, br t, *J* 10.4, C(1′)H_B), 3.26 (1H, t, *J* 8.3 C(2)*H*), 2.14 (1H, s, C(1)O*H*), 1.99–1.37 (6H, m, (CH_2)$_3$), 1.35 (3H, d, *J* 6.9, C(α)*Me*); δ_C (125 MHz, $CDCl_3$) 142.8, 139.2 (*Ph*$_{ipso}$), 129.1, 128.8, 128.5, 128.1, 127.5 (*Ph*$_{o\text{-},m\text{-},p\text{-}}$), 81.5 (*C*(*1*)), 67.5 (*C*(α)H), 67.3 (*C*(*1′*)H$_2$OH), 53.8 (*C*(2)H), 53.2 (N*C*H$_2$), 35.0, 28.0, 22.2 ((*C*H$_2$)$_3$), 10.6 (C(α)*Me*); HRMS (CI$^+$) $C_{21}H_{28}N_1O_2$ requires 326.2120; found 326.2123.

4.24. Preparation of (2*R*,α*R*)-2-(*N*-benzyl-*N*-α-methylbenzylamino)cyclopentanone 28

Following general procedure 3, **27** (45 mg, 0.14 mmol) and H_5IO_6 (35 mg, 0.15 mmol) gave **28** (35 mg, 85%) as a colourless oil. This was shown by ^{1}H 500 MHz NMR spectroscopic analysis to contain two diastereoisomers in 88% d.e.; $[\alpha]_D^{24} = -11.3$ (*c* 0.75, $CHCl_3$); ν_{max} (film) 1743 (C=O); δ_H (500 MHz, $CDCl_3$) 7.53–7.19 (10H, m, *Ph*), 4.15 (1H, q, *J* 6.8, C(α)*H*), 3.73 (2H, app s, NCH_2), 3.18 (1H, dd, *J* 11.9, *J* 7.9, C(2)*H*), 2.19 (1H, m, C(5)H_ACO), 2.09 (1H, m, C(5)H_BCO), 1.90 (2H, m, C(3)H_2), 1.57 (2H, m, C(4)H_2), 1.32 (3H, d, *J* 6.8, C(α)*Me*); δ_C (125 MHz, $CDCl_3$) 219.4 (*C*=O), 141.1, 129.0 (*Ph*$_{ipso}$), 128.5, 128.3, 128.1, 127.4, 126.7 (*Ph*$_{o\text{-},m\text{-},p\text{-}}$), 66.5 (*C*(α)H), 57.8 (*C*(*2*)H), 52.2 (N*C*H$_2$), 36.8 (*C*(*5*)H$_2$), 27.4 (*C*(*3*)H$_2$), 18.3 (*C*(*4*)H$_2$), 17.6 (C(α)*Me*); *m*/*z* (APCI$^+$) 294, (MH$^+$, 10%); HRMS (CI$^+$, MH$^+$) $C_{20}H_{24}NO$ requires 294.1858; found 294.1852.

4.25. Preparation of (2*R*,3*R*,α*R*)- and (2*S*,3*R*,α*R*)-*tert*-butyl 2-hydroxy-2-methyl-3-(*N*-benzyl-*N*-α-methylbenzylamino)butanoate 30 and 42

Following general procedure 1, *tert*-butyl tiglate[22] **29** (0.78 g, 2.5 mmol) in THF (10 ml), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (0.85 g, 4.0 mmol) in THF (10 ml), *n*-BuLi (2.5 M, 1.6 ml, 3.9 mmol) and (1*R*)-(−)-(10-camphorsulfonyl)oxaziridine (1.2 g, 5 mmol), gave, after chromatographic purification (hexane:Et_2O, 3:1) gave **30** (458 mg, 48%) and **42** (152 mg, 16%) as colourless oils.

Data for **30**: $[\alpha]_D^{22} = -36.8$ (*c* 2.0, $CHCl_3$); ν_{max} (film) 1716 (C=O); δ_H (400 MHz, $CDCl_3$) 7.58–7.25 (10H, m, *Ph*), 4.23 (1H, AB, *J* 14.3, NCH_B), 4.10 (1H, q, J6.7, C(α)*H*), 3.69 (1H, AB, *J* 14.3, NCH_A), 3.67 (1H, s, O*H*), 3.09 (1H, q, *J* 6.9, C(3)*H*), 1.47 (9H, s, OC*Me*$_3$), 1.46 (3H, d, *J* 6.7, C(α)*Me*), 1.27 (3H, d, *J* 6.9, C(4)H_3), 1.00 (3H, s, C(2)*Me*); δ_C (100 MHz, $CDCl_3$) 176.1 (*C*=O), 143.4, 140.8 (Ph$_{ipso}$), 129.2, 128.2, 128.0, 127.7, 126.7, 126.6 (Ph$_{o\text{-},m\text{-},p\text{-}}$), 81.4 (*C*(2)), 77.5 (O*C*Me$_3$), 55.8 (*C*(α)H), 55.4 (*C*(3)), 51.2 (N*C*H$_2$), 27.6 (OC*Me*$_3$), 24.1 (C(2)*Me*), 12.1 (*C*(α)Me), 11.2 (*C*(4)H$_3$); HRMS (CI$^+$) $C_{24}H_{34}NO_3$ requires 384.2539; found 384.2530.

Data for **42**: ν_{max} (film) 1717 (C=O); δ_H (400 MHz, $CDCl_3$) 7.47–7.09 (10H, m, *Ph*), 3.99 (1H, q, *J* 6.9, C(α)*H*), 3.95 (1H, AB, *J* 14.9, NCH_B), 3.62 (1H, AB, *J* 14.9, NCH_A), 3.28 (1H, q, *J* 7.0, C(3)*H*), 3.20 (1H, s, O*H*), 1.43 (9H, s, OC*Me*$_3$), 1.20 (3H, d, *J* 6.9, C(α)*Me*), 1.10 (3H, s, C(2)*Me*); 0.88 (3H, d, *J* 6.9, C(4)H_3); δ_C (100 MHz, $CDCl_3$) 179.4 (*C*=O), 142.6, 142.4 (*Ph*$_{ipso}$), 128.3, 128.2, 128.1, 127.0, 126.5 (*Ph*$_{o\text{-},m\text{-},p\text{-}}$), 81.7 (*C*(2)), 78.8 (O*C*Me$_3$), 59.6 (*C*(α)H, *C*(3)H), 50.0 (N*C*H$_2$), 28.1 (OC*Me*$_3$), 23.7 (C(2)*Me*), 17.8 (*C*(α)Me), 10.5 (*C*(4)H$_3$); HRMS (CI$^+$) $C_{24}H_{34}NO_3$ requires 384.2539; found 384.2532.

4.26. Preparation of (2*R*,3*R*,α*R*)-2-hydroxy-2-methyl-3-(*N*-benzyl-*N*-α-methylbenzylamino)butanol 31

Following general procedure 2, **30** (192 mg, 0.5 mmol) and $LiAlH_4$ (0.5 ml) in THF (3 ml) gave, after chro-

matographic purification (Et_2O), **31** (144 mg, 92%) as a colourless oil; $[\alpha]_D^{22} = -14.5$ (*c* 0.6, $CHCl_3$); ν_{max} (film) 3402 (OH); δ_H (500 MHz, $CDCl_3$) 7.46–7.19 (10H, m, *Ph*), 4.01 (1H, d, *J* 13.9, NCH_A), 3.98 (1H, q, *J* 6.9, C(α)*H*), 3.69 (1H, d, *J* 13.9, NCH_B), 3.52, 3.17 (2×1H, d, *J* 10.8, C(1)H_2OH), 2.93 (1H, q, *J* 7.2, C(3)*H*), 1.42 (3H, d, *J* 6.9, C(α)*Me*), 1.27 (3H, d, *J* 7.2, C(4)H_3), 0.96 (3H, s, C(2)*Me*); δ_C (125 MHz, $CDCl_3$) 143.0, 140.2 (Ph_{ipso}), 128.8, 128.6, 128.4, 128.2, 127.5, 127.4 ($Ph_{o-,m-,p-}$), 73.4 (*C*(2)), 67.1 (*C*(1)H_2OH), 56.6 (*C*(α)H), 56.2 (*C*(3)H), 52.0 (N*C*H_2), 21.7 (C(2)*Me*), 11.9 (*C*(4)H_3), 10.7 (C(α)*Me*); HRMS (CI^+) $C_{20}H_{28}NO_2$ requires 314.2120; found 314.2130.

4.27. Preparation of (3*R*,α*R*)-3-(*N*-benzyl-*N*-α-methylbenzylamino)butan-2-one 32

Following general procedure 3, **31** (27 mg, 0.1 mmol) and H_5IO_6 (22 mg, 0.10 mmol) gave **32** (19 g, 79%) as a colourless oil. This was shown by ^{1}H 500 MHz NMR spectroscopic analysis to contain two diastereoisomers in 88% d.e.; $[\alpha]_D^{21} = -74.0$ (*c* 0.5, $CHCl_3$); ν_{max} (film) 1713 (C=O); δ_H (500 MHz, $CDCl_3$) 7.41–7.26 (10H, m, *Ph*), 4.04 (1H, q, *J* 6.8, C(α)*H*), 3.82 (2H, app s, NCH_2), 3.46 (1H, q, *J* 6.9, C(2)*H*), 1.94 (3H, s, COCH_3), 1.42 (3H, d, *J* 6.8, C(α)*Me*); 1.25 (3H, d, *J* 6.9, C(3)H_3); δ_C (125 MHz, $CDCl_3$) 211.2 (*C*=O), 144.4, 141.1 (Ph_{ipso}), 129.1, 128.7, 128.6, 128.3, 127.4 ($Ph_{o-,m-,p-}$), 61.8 (*C*(2)H), 58.2 (*C*(α)H), 51.5 (N*C*H_2), 27.9 (CO*C*H_3), 16.7 (C(α)*Me*), 12.9 (*C*(3)H_3); HRMS (CI^+) $C_{19}H_{24}NO$ requires 282.1856; found 282.1850.

4.28. Preparation A of (2*R*,α*R*)-2-(*N*-benzyl-*N*-α-methylbenzylamino)propanoic acid 33

20 (81 mg, 0.30 mmol) was dissolved in acetone (10 ml) and cooled to 0°C before the addition of Jones reagent (0.13 ml, 0.33 mmol) and the solution stirred at 0°C for 2 h before the addition of isopropyl alcohol (1 ml). Dissolution in ether (50 ml), filtration through Celite® followed by concentration in vacuo afforded an oil which was purified by chromatography on silica (hexane–Et_2O, 3:1–1:1) to afford **33** as a colourless oil (42 mg, 48%). The Celite® was washed with MeOH to afford an oil, purified by chromatography (hexane–ether, 1:1) to afford (*R*)-*N*-benzyl-*N*-α-methylbenzylamine as an oil (19 mg, 29%).

4.29. Preparation of (2*R*,α*R*)-2-(*N*-benzoyl-*N*-α-methylbenzylamino)propanoic acid 34

$NaIO_4$ (333 mg, 1.56 mmol) and $RuCl_3$ (1.8 mg, 0.03 mmol) were dissolved in a mixture of CCl_4 (2 ml), MeCN (3 ml) and H_2O (1 ml) before the addition of **121** (100 mg, 0.38 mmol) in CCl_4 (0.5 ml) and stirred for 2 h at rt. The crude reaction mixture was partitioned between DCM (20 ml) and water (20 ml), the organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (2×20 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to afford a brown oil which was purified by chromatography on silica (Et_2O to Et_2O–methanol, 10:1) affording **34** as a colourless oil (70 mg, 63%); $[\alpha]_D^{24} = +81.2$ (*c* 1.0, $CHCl_3$); ν_{max} (film) 2992 (C-H), 1716 (CO_2H), 1634 (COPh); δ_H (500 MHz, toluene, 85°C) 7.38–7.01 (10H, m, *Ph*), 5.00 (1H, q, *J* 6.8, C(α)*H*), 3.59 (1H, q, $J_{6.9}$, C(2)*H*), 1.62 (3H, d, *J* 6.9, C(3)H_3), 1.25 (3H, d, *J* 6.8, C(α)*Me*); δ_C (125 MHz, $CDCl_3$) 174.5 (*C*O_2H), 172.9 (*C*OPh) 136.3 (Ph_{ipso}), 130.5, 129.3, 129.0, 128.6, 127.9 126.8 ($Ph_{o-,m-,p-}$), 58.1 (*C*(2)H), 54.1 (*C*(α)H), 18.5, 16.8 (C(α)*Me*, *C*(3)H_3); HRMS (CI^+) $C_{18}H_{20}NO_3$ requires 298.1443; found 298.1450.

4.30. Preparation B of (2*R*,α*R*)-2-(*N*-benzyl-*N*-α-methylbenzylamino)propanoic acid 33

Following general procedure 4, **20** (248 mg, 0.93 mmol) and $NaClO_2$ (92.5 mg, 1.0 mmol) gave, after purification by chromatography on silica (hexane–Et_2O, 3:1–1:1), **33** (142 mg, 54%) as a colourless oil; $[\alpha]_D^{24} = +27.7$ (*c* 1.0, $CHCl_3$); ν_{max} (film) 1715 (C=O); δ_H (500 MHz, $CDCl_3$) 7.45–7.22 (10H, m, *Ph*), 4.15 (1H, q, *J* 6.8, C(α)*H*), 3.91 (1H, AB, *J* 13.6, NCH_B), 3.83 (1H, AB, *J* 14.3, NCH_A), 3.56 (1H, q, *J* 7.3, C(2)*H*), 1.49 (3H, d, *J* 7.3, C(3)H_3), 1.46 (3H, d, *J* 6.8, C(α)*Me*); δ_C (125 MHz, $CDCl_3$) 174.7 (*C*O), 140.1, 137.4 (Ph_{ipso}), 129.0, 128.8, 128.0, 127.9 127.5 ($Ph_{o-,m-,p-}$), 57.0 (*C*(2)H), 55.9 (*C*(α)H), 51.4 (N*C*H_2), 13.9, 13.3 (C(α)*Me*, *C*(3)H_3); HRMS (CI^+) $C_{18}H_{22}NO_2$ requires 284.1651; found 284.1651.

4.31. Preparation of (2*R*,α*R*)-2-(*N*-benzyl-*N*-α-methylbenzylamino)-4-methylpentanoic acid 35

Following general procedure 4, **22** (295 mg, 0.96 mmol) and $NaClO_2$ (95 mg, 1.05 mmol) gave, after purification by chromatography on silica (hexane–Et_2O, 2:1–1:1), **35** (198 mg, 64%) as a colourless oil; $[\alpha]_D^{25} = +28.9$ (*c* 1.0, $CHCl_3$); ν_{max} (film) 1704 (C=O); δ_H (500 MHz, $CDCl_3$) 7.56–7.30 (10H, m, *Ph*), 4.17 (1H, q, *J* 6.8, C(α)*H*), 4.05 (1H, AB, *J* 15.1, NCH_B), 3.99 (1H, AB, *J* 15.1, NCH_A), 3.50 (1H, dd, $J_{2,3A}$ 7.6, $J_{2,3B}$ 6.9, C(2)*H*), 2.00 (1H, app sept, *J* 6.7, (C(4)*H*), 1.76 (1H, m, C(4)*H*), 1.58 (1H, m, C(4)*H*), 1.41 (3H, d, *J* 6.8, C(α)*Me*), 0.92 (3H, d, *J* 6.7, C(4)CH_3), 0.88 (3H, d, *J* 6.7, C(4)CH_3); δ_C (62.5 MHz, $CDCl_3$) 178.3 (*C*=O), 143.3, 140.6 (Ph_{ipso}), 129.4, 129.1, 129.0, 128.6, 128.2, 128.0, 127.6 ($Ph_{o-,m-,p-}$), 59.9, 59.3 (*C*(α)H, *C*(2)H), 52.1 (N*C*H_2) 39.4 (*C*(3)H_2), 26.0 (*C*(4)H), 22.8 (C(4)(*C*H_3)$_2$), 18.7 (C(α)*Me*); HRMS (CI^+) $C_{21}H_{28}NO_2$ requires 326.2120; found 326.2123.

4.32. Preparation of (2*R*,α*R*)-2-(*N*-benzyl-*N*-α-methylbenzylamino)nonanoic acid 36

Following general procedure 4, **23** (220 mg, 0.63 mmol) and $NaClO_2$ (62 mg, 0.69 mmol) gave, after purification by chromatography on silica (hexane–Et_2O, 2:1–1:1), **36** (156 mg, 68%) as a colourless oil; $[\alpha]_D^{25} = +4.3$ (*c* 1.0, $CHCl_3$); ν_{max} (film) 1704 (C=O); δ_H (400 MHz, $CDCl_3$) 7.47–7.25 (10H, m, *Ph*), 4.13 (1H, q, *J* 6.9, C(α)*H*), 4.02 (1H, AB, *J* 15.0, NCH_B), 3.94 (1H, AB, *J* 15.0, NCH_A), 3.37 (1H, t, *J* 6.0, C(2)*H*), 1.84 (1H, m, C(3)H_A), 1.68 (1H, m, C(3)H_B), 1.37 (3H, d, *J* 6.9,

C(α)*Me*), 1.34–1.21 (10H, m, $((CH_2)_5)$), 0.91 (3H, t, *J* 6.9, *C*(9)H_3); δ_C (100 MHz, $CDCl_3$) 177.5 (*C*=O), 142.7, 140.3 (Ph_{ipso}), 128.5, 128.2, 127.7, 127.5, 127.2 ($Ph_{o-,m-,p-}$), 60.9 (*C*(α)H), 59.3 (*C*(2)H), 51.7 (N*C*H_2), 31.8, 29.7, 29.5, 29.1, 27.5, 22.6, $((CH_2)_6)$, 18.2 (C(α)*Me*), 14.1 (*C*(9)H_3); HRMS (CI$^+$) $C_{24}H_{34}NO_2$ requires 368.2590; found 368.2601.

4.33. Preparation of (2*R*,α*R*)-2-phenyl-2-(*N*-benzyl-*N*-α-methylbenzylamino)ethanoic acid 37

Following general procedure 4, **24** (221 mg, 0.67 mmol) and $NaClO_2$ (70 mg, 0.77 mmol) gave, after purification by chromatography on silica (hexane–Et_2O, 3:1–2:1), **37** (156 mg, 64%) as a colourless oil; $[\alpha]_D^{25} = -12.8$ (*c* 1.0, $CHCl_3$); ν_{max} (film) 1717 (C=O); δ_H (500 MHz, $CDCl_3$) 7.44–7.24 (15H, m *Ph*), 4.75 (1H, s, C(2)*H*), 4.22 (1H, q, *J* 6.9, C(α)*H*), 4.02 (1H, AB, *J* 14.4, N*C*H_B), 3.78 (1H, AB, *J* 14.4, N*C*H_A), 1.28 (3H, d, *J* 6.9, C(α)*Me*); δ_C (50 MHz, $CDCl_3$) 181.1 (*C*=O), 148.6, 145.9, 142.3 (Ph_{ipso}), 137.4, 136.1, 135.9, 135.8, 135.7, 135.6, 135.3, 135.1, 134.8 ($Ph_{o-,m-,p-}$), 73.8 (*C*(2)H), 66.4 (*C*(α)H), 59.0 (N*C*H_2), 23.6 (C(α)*Me*); HRMS (CI$^+$) $C_{23}H_{24}NO_2$ requires 346.1807; found 346.1812.

4.34. Preparation of (*R*)-alanine hydrochloride 38

Following representative procedure 5, **33** (184 mg, 0.65 mmol) and Pd–C (184 mg, 10 mol%) gave **38** as a white solid (79 mg, 92%); mp 202°C, {lit.[23] 207–209°C); $[\alpha]_D^{25} = -8.2$ (*c* 1.00, H_2O), {lit.[24] (*ent*) $[\alpha]_D^{20} = +6.3$ (*c* 1.2, H_2O)}; δ_H (250 MHz, D_2O) 3.96 (1H, q, *J* 7.4, C(2)*H*), 1.42 (3H, d, *J* 7.4 Hz, C(3)H_3), consistent with that recorded in the literature.[24]

4.35. Preparation of (*R*)-leucine hydrochloride 39

Following representative procedure 5, **35** (77 mg, 0.24 mmol) and Pd–C (77 mg, 10 mol%) gave **39** as a white solid (37 mg, 93%); mp 250°C dec.; $[\alpha]_D^{25} = -3.2$ (*c* 0.5, H_2O); {lit.[24] (*ent*) $[\alpha]_D^{20} = +2.8$ (*c* 0.61, H_2O)}; δ_H (500 MHz, D_2O) 3.97 (1H, m, C(2)*H*), 1.75 (1H, app quintet, *J* 5.9, C(4)*H*), 1.64 (2H, m, C(3)H_2), 0.87 (3H, d, *J* 6.2, $(CH_3)_2$CH), 0.85 (3H, d, *J* 6.2, $(CH_3)_2$CH); consistent with that recorded in the literature.[24]

4.36. Preparation of (*R*)-2-amino-nonanoic acid hydrochloride 40[25]

Following representative procedure 5, **36** (42 mg, 0.11 mmol) and Pd–C (42 mg, 10 mol%) gave **40** as a white solid (23 mg, 96%); mp 251°C, dec.; $[\alpha]_D^{22} = -25.0$ (*c* 0.5, AcOH); δ_H (500 MHz, D_2O) 3.41 (1H, m, C(2)*H*), 1.71 (2H, m, C(3)H_2), 1.17 (10H, m, $(CH_2)_5$), 0.73 (3H, t, *J* 7.1, C(9)H_3).

4.37. Preparation of (*R*)-phenylglycine hydrochloride 41

Following representative procedure 5, **37** (69 mg, 0.2 mmol) and Pd–C (69 mg, 10 mol%) gave **41** as a white solid (34 mg, 91%); mp 250°C dec., lit.[23] 254–256°C dec.; $[\alpha]_D^{25} = -105$ (*c* 1.0, H_2O), {lit.[23] $[\alpha]_D^{25} = -112.3$ (*c* 0.98, H_2O)}; δ_H (500 MHz, D_2O) 7.49–7.45 (5H, m, *Ph*), 5.12 (1H, s, C(2)*H*), consistent with that recorded in the literature.[23]

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12. The minor diastereoisomer was assumed to be the *syn*-α-hydroxy-β-amino ester, and was isolated in 16% yield, giving an overall yield of 64%.
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