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Parallel kinetic resolution of *tert*-butyl (*RS*)-6-alkyl-cyclohex-1-ene-carboxylates for the asymmetric synthesis of 6-alkyl-substituted cishexacin derivatives

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ABSTRACT

Excellent levels of enantiorecognition are displayed by *tert*-butyl (*RS*)-6-*n*-alkyl-cyclohex-1-ene-carboxylates in mutual kinetic resolutions with lithium (*RS*)-*N*-benzyl-*N*-(α-methylbenzyl)amide. Therefore a 50:50 pseudoenantiomeric mixture of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide and lithium (*R*)-*N*-3,4-dimethoxybenzyl-*N*-(α-methylbenzyl)amide allows their efficient parallel kinetic resolution, affording differentially protected 6-*n*-alkyl-cishexacin derivatives in high yield and >95% de. N-Debenzylation and ester hydrolysis give access to the corresponding homochiral 6-*n*-alkyl-substituted cishexacin derivatives.

1. Introduction

There has been considerable interest in the secondary structural characteristics of short (typically fewer than eight residues) oligomers comprising β-amino acids.[1] Within this arena, oligomers of the diastereoisomers of the simple cyclic β-amino acids, 2-amino-cyclopentane-carboxylic acids (cispentacin and transpentacin) and 2-amino-cyclohexane-carboxylic acids (cishexacin and transhexacin) have been shown to adopt well-defined secondary structures in solution and in the solid state.[2,3] In order to enhance the structural diversity of monomeric cispentacin and transpentacin derivatives available for both secondary structural[2] and bioactivity studies,[4] we recently reported the efficient kinetic and parallel kinetic resolution of a range of 3-alkyl-, 3-oxy- and 5-alkyl-substituted cyclopent-1-ene-carboxylates,[5] utilising the conjugate addition of either homochiral or a pseudoenantiomeric mixture of homochiral lithium amides,[6] respectively, for the asymmetric synthesis of the corresponding homochiral 3- and 5-substituted cispentacin and transpentacin derivatives. In these systems, high levels of substrate bias for conjugate addition *anti* to the 3- or 5-substituent, coupled with the exceptionally high facial preferences of lithium amides **1** and **2**,[7] allowed highly selective resolutions to be achieved. High levels of facial selectivity upon kinetic protonation of the intermediate enolates, *anti* to the newly installed nitrogen substituent,[5,8] allowed ready access to single diastereoisomers of both enantiomeric series of 3- or 5-substituted 2-amino-cyclopentane-carboxylates, which were easily separable by chromatography due to the differing polarities of the *N*-benzyl and *N*-3,4-dimethoxybenzyl protecting groups (Scheme 1).

We wished to extend this versatile protocol to encompass the synthesis of substituted cishexacin derivatives, via parallel kinetic resolution of a substituted *tert*-butyl cyclohex-1-ene-carboxylate upon treatment with a 50:50 mixture of pseudoenantiomeric lithium amides, and report herein our investigations within this area concerning the preparation of 6-substituted cishexacin derivatives.

2. Results and discussion

When investigating parallel kinetic resolutions,[5d–h] we have promulgated the idea that it is prudent to follow a strategy of first evaluating the level of substrate control—in this system through the addition of an achiral lithium amide to the racemic α,β-unsaturated ester. In cases where high levels of substrate control are observed, the conjugate addition of a racemic lithium amide to the racemic α,β-unsaturated ester (mutual kinetic resolution) may then be performed, allowing the selectivity factor *E* to be directly determined in the absence of deleterious mass action effects.[9] Having established the maximum levels of enantiorecognition attainable, parallel kinetic resolution utilising the conjugate addition of a 50:50 mixture of the pseudoenantiomeric, homochiral lithium amides, lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **1** and lithium (*R*)-*N*-3,4-dimethoxybenzyl-*N*-(α-methylbenzyl)amide **2** can be performed.

2.1. Preparation of 6-alkyl-cyclohex-1-ene-carboxylates

The synthesis of a range of *tert*-butyl 6-alkyl-cyclohex-1-ene carboxylates **6**–**11** was accomplished from glutaraldehyde.[5f,10]

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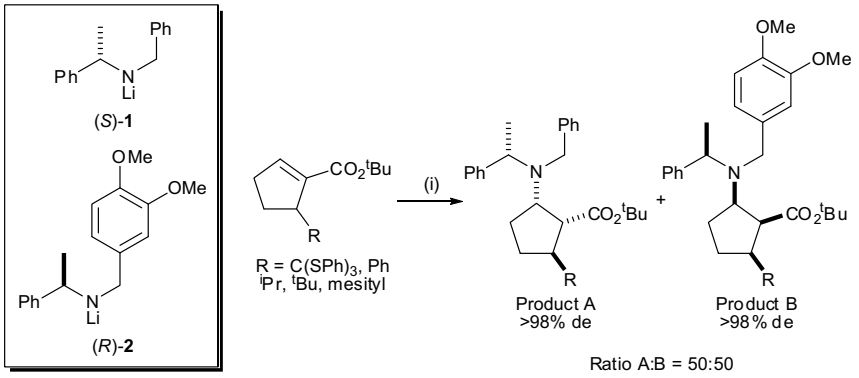
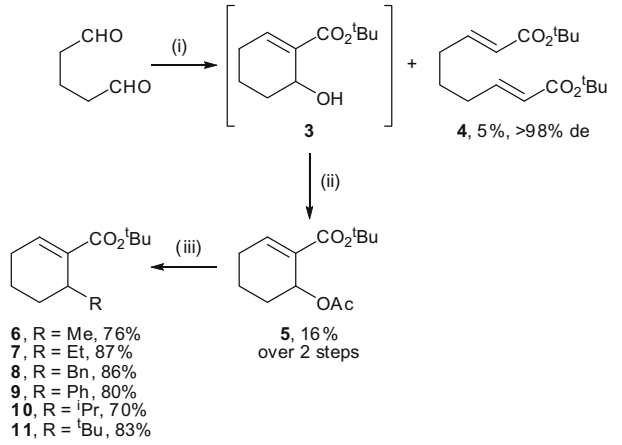


Scheme 1. Reagents and conditions: (i) lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*S*)-**1**, lithium (*R*)-*N*-3,4-dimethoxybenzyl-*N*-(α-methylbenzyl)amide (*R*)-**2**, THF, −78 °C, 2 h, then NH_4Cl (satd, aq).

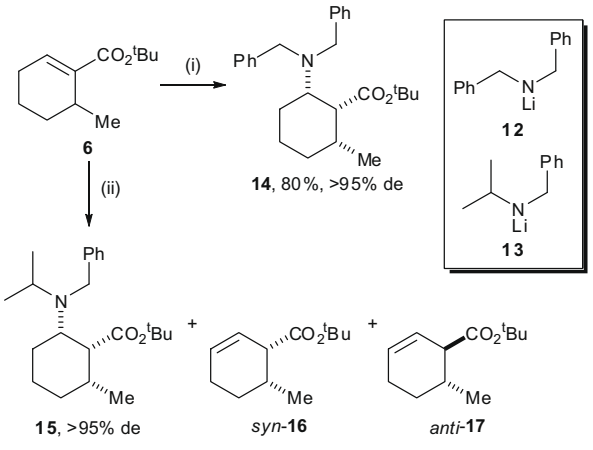
Under optimised conditions, treatment of glutaraldehyde with *tert*-butyl diethylphosphonoacetate in a biphasic 7 M aq K_2CO_3/DCM mixture in the presence of Aliquat® 336 gave a mixture of cyclic α,β-unsaturated ester **3** and diester **4**. Separation by chromatography gave **4** in 5% yield as a single diastereoisomer, and **3** as a mixture with Aliquat® 336. This mixture was treated with acetic anhydride, with subsequent purification giving acetate **5** in 16% yield over two steps from glutaraldehyde. Copper-mediated Grignard alkylation of **5** allowed access to a range of *tert*-butyl 6-alkyl-cyclohex-1-ene carboxylates **6**–**11** (Scheme 2).



Scheme 2. Reagents and conditions: (i) $(EtO)_2POCH_2CO_2{}^tBu$, K_2CO_3 (7 M, aq), Aliquat® 336, DCM, rt, 72 h; (ii) Ac_2O, Et_3N, DMAP, DCM, rt, 16 h; (iii) RMgCl, CuI, THF, −78 °C to rt, 1 h.

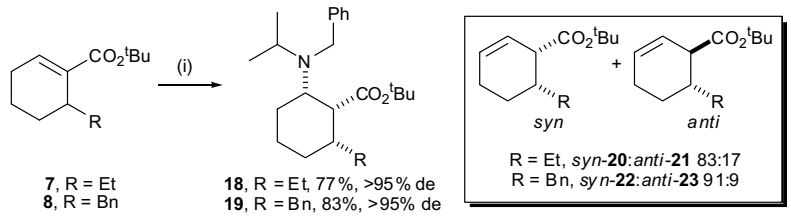
2.2. Evaluation of substrate control

With 6-alkyl-cyclohex-1-ene-carboxylates **6**–**11** in hand, the inherent levels of substrate diastereofacial control were evaluated via the conjugate addition of achiral lithium amides. Lithium dibenzylamide **12**[5b,c,e,g,h,11] and lithium *N*-benzyl-*N*-isopropylamide **13**[5g,h] were investigated, the latter being employed as it has been previously shown by us to very closely mimic the reactivity of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **1**. Conjugate addition of lithium dibenzylamide **12** to 6-methyl-substituted α,β-unsaturated ester **6** gave β-amino ester **14** as a single diastereoisomer (>95% de)[12] and trace amounts (<5%) of β,γ-unsaturated esters *syn*-**16** and *anti*-**17** (in the ratio of 60:40), which arise from γ-deprotonation of α,β-unsaturated ester **6** by the lithium amide, rather than conjugate addition. The relative configuration within the major diastereoisomeric β,γ-unsaturated ester **16** was tentatively assigned as *syn* by analogy with a related system (vide infra). Chromatographic purification gave **14** in 80% yield and >95% de. The relative configuration within **14** was assigned by ^3J ^1H NMR coupling constant analysis, assuming that in solution **14** adopts a chair conformation which places the bulky *N*,*N*-dibenzylamino substituent in an equatorial position. Conjugate addition of lithium *N*-benzyl-*N*-isopropylamide **13** to α,β-unsaturated ester **6** also proceeded in >95% de, to give β-amino ester **15**, but was accompanied by 15% of competing γ-deprotonation to give a 60:40 mixture of *syn*-**16** and *anti*-**17**. Chromatography gave an 85:15 mixture of β-amino ester **15** and the products of γ-deprotonation (*syn*-**16** and *anti*-**17**). The relative all-*syn* configuration within β-amino ester **15** was assigned on the basis of ^3J ^1H NMR coupling constant analysis (Scheme 3).



Scheme 3. Reagents and conditions: (i) lithium dibenzylamide **12** (4 equiv), THF, −78 °C, 3 h, then NH_4Cl (satd, aq); (ii) lithium *N*-benzyl-*N*-isopropylamide **13** (4 equiv), THF, −78 °C, 3 h, then NH_4Cl (satd, aq).

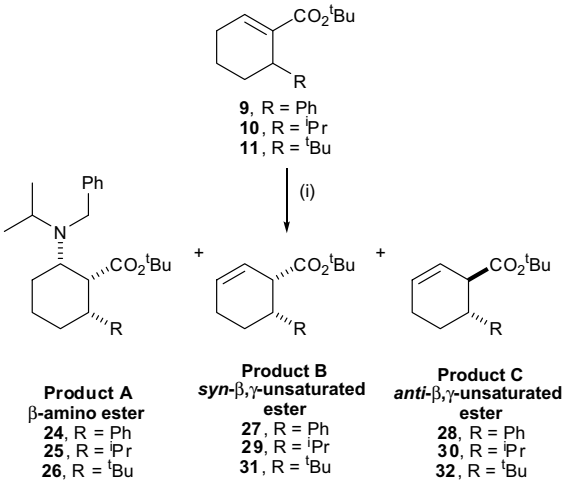
Having demonstrated that the 6-methyl-substituent within **6** offers excellent levels of substrate control upon conjugate addition of both lithium dibenzylamide **12** and lithium *N*-benzyl-*N*-isopropylamide **13**, the addition of lithium *N*-benzyl-*N*-isopropylamide **13** to the range of 6-substituted α,β-unsaturated esters **7**–**11** was investigated. Addition to 6-ethyl **7** and 6-benzyl **8** gave, in each case, the corresponding β-amino esters **18** and **19** in >95% de, along with ~10% of the corresponding *syn*- and *anti*-diastereoisomers of the β,γ-unsaturated ester products of γ-deprotonation **20**–**23**. Chromatography gave **18** and **19** in 77% and 83% yields, respec-



Scheme 4. Reagents and conditions: (i) lithium *N*-benzyl-*N*-isopropylamide **13** (4 equiv), THF, −78 °C, 3 h, then NH_4Cl (satd, aq).

tively. ^3J ^{1}H NMR coupling constant analysis facilitated the assignment of the relative 1,2-*syn*-1,6-*syn*-configuration within **18** and **19** (Scheme 4).

Attempted conjugate addition of lithium *N*-benzyl-*N*-isopropylamide **13** to 6-phenyl **9**, 6-isopropyl **10** or 6-*tert*-butyl **11** gave mixtures comprising starting material, the corresponding 1,4-addition products **24**–**26** (>95% de) and the diastereoisomers of the corresponding β,γ-unsaturated esters **27**–**32**, in varying ratios. In the case of 6-*tert*-butyl-substituted β,γ-unsaturated esters **31** and **32**, ^3J ^{1}H NMR coupling constant analysis allowed assignment of the relative *syn*-configuration of the major diastereoisomer **31** and the relative *anti*-configuration of the minor diastereoisomer **32**, assuming in both cases that a half-chair conformation is adopted with the *tert*-butyl group occupying a pseudoequatorial site. The relative *syn*-configuration of the major diastereoisomeric β,γ-unsaturated esters **16**, **20**, **22**, **27** and **29** were therefore tentatively assigned by analogy. In an attempt to favour the conjugate addition reaction of lithium *N*-benzyl-*N*-isopropylamide **13** to α,β-unsaturated esters **9**–**11**, iterative experiments involving changes to reaction times, concentration and equivalents of lithium amide were performed, but yielded similar results. Due to the substantial competing formation of β,γ-unsaturated esters **27**–**32** in these cases, it was envisaged that these substrates would not be amenable to further investigation into their mutual or parallel kinetic resolution (Scheme 5).



R	conversion %	ratio A:B:C
Ph	100	78:13:9
^{i}Pr	74	41:35:24
^{t}Bu	56	13:70:17

Scheme 5. Reagents and conditions: (i) lithium *N*-benzyl-*N*-isopropylamide **13** (4 equiv), THF, −78 °C, 3 h, then NH_4Cl (satd, aq).

The β-amino ester products **14**, **15**, **18** and **19** formed upon conjugate addition of lithium amides **12** and **13** to α,β-unsaturated esters **6**–**8** are consistent, in each case, with the 6-alkyl substituent showing complete diastereofacial control, with preferential addition of the lithium amide occurring *syn* to the stereocontrolling 6-alkyl substituent. This predilection presumably arises due to minimisation of 1,2-strain between the ester group and adjacent C(6)-alkyl group, forcing the latter into a pseudo-axial position of a half-chair conformation **33**. Favoured axial attack of lithium amides **12** and **13** and subsequent protonation *anti* to the amino group[5,8] afford the all *syn* product. In the case of **9**–**11**, however, the bulkier, α-branched substituents presumably block the *syn* face of the α,β-unsaturated ester, thus retarding the conjugate addition reaction. Alignment of the pseudoaxial C−H σ-bond of C(3) with the π-system of the α,β-unsaturated ester in conformation **33** accounts for the alternative, ready γ-deprotonation reaction occurring in this system. Kinetic protonation of the intermediate dienolate *anti* to the 6-alkyl group accounts for the modest preference for formation of the *syn*-diastereoisomer of the corresponding β,γ-unsaturated ester (Fig. 1).

Having demonstrated that *tert*-butyl 6-alkyl-cyclohex-1-enecarboxylates **6**–**8** demonstrate very high levels of substrate control upon conjugate addition of lithium *N*-benzyl-*N*-isopropylamide **13**, the mutual kinetic resolution of **6**–**8** with lithium (*RS*)-*N*-benzyl-*N*-(α-methybenzyl)amide (*RS*)-**1** was next investigated in order to determine the maximum value of the stereoselectivity factor *E*.[9]

2.3. Mutual kinetic resolution

In mutual kinetic resolutions, mass action effects are negated and the selectivity factor *E* is independent of the reaction conversion, and is equivalent to the ratio of products.[9] The conjugate addition of racemic lithium amide (*RS*)-**1** to 6-methyl **6** was initially investigated and, after quenching with satd aq NH_4Cl, β-amino ester **34** was formed in >95% de, consistent with E >40.[9] The conjugate addition reaction was accompanied by trace amounts (<5%) of competing γ-deprotonation leading to β,γ-unsaturated esters *syn*-**16** and *anti*-**17** (in the ratio 60:40). Purification by flash chromatography gave β-amino ester **34** in 85% isolated yield and >95% de (Scheme 6). The relative (1*RS*,2*SR*,6*RS*,α*SR*)-configuration within **34** was unambiguously established by single crystal X-ray crystallographic analysis (Fig. 2). This analysis also confirmed that the relative configurations of the C(2) and *N*-α-methylbenzyl stereocentres were consistent with the diastereofacial preference of both the chiral lithium amide **1** (reagent) and the chiral α,β-unsaturated ester **6** (substrate). The mutual kinetic resolutions of 6-ethyl **7** and 6-benzyl **8** with lithium amide (*RS*)-**1** were investigated and gave, in each case, single diastereoisomeric β-amino ester products **35** and **36**, respectively (>95% de, consistent with E >40),[9] and the β,γ-unsaturated esters **20**–**23** (<5% in both cases). Chromatography gave **35** and **36** in good yield (Scheme 6). In each case, the relative configuration [(1*RS*,2*SR*,6*RS*,α*SR*)-**35** and (1*RS*,2*SR*,6*SR*,α*SR*)-**36**] was assigned by analogy to that unambiguously proven for β-amino ester **34**; ^3J ^{1}H NMR coupling constant analyses of **35** and **36** were supportive of these assignments for the C(1),

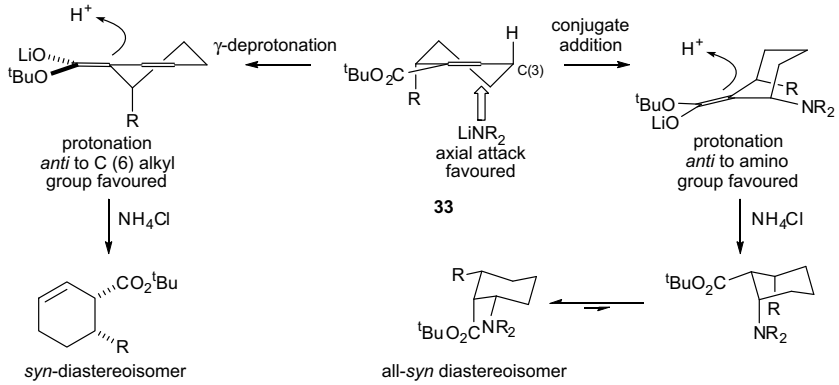
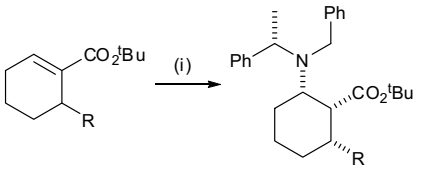


Figure 1. Mnemonic depicting lithium amide conjugate addition to and γ-deprotonation of 6-alkyl-cyclohex-1-enecarboxylates **6**–**11**.



6, R = Me
7, R = Et
8, R = Bn

34, R = Me, 85%, >95% de
35, R = Et, 76%, >95% de
36, R = Bn, 84%, >95% de

Scheme 6. Reagents and conditions: (i) lithium (*RS*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*RS*)-**1** (4 equiv) THF, −78 °C, 3 h, then NH_4Cl (satd, aq).

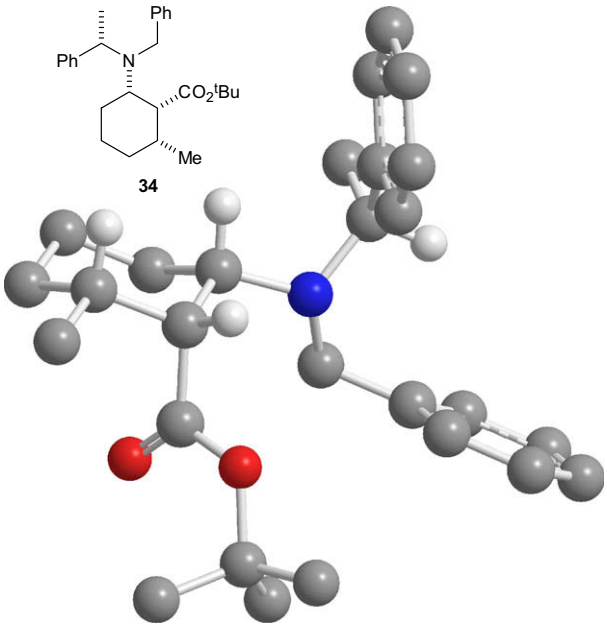
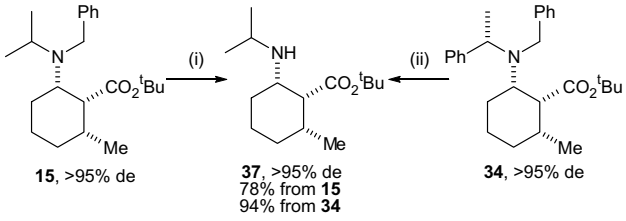


Figure 2. Chem 3D representation of the X-ray crystal structure of **34** (some H atoms removed for clarity).

C(2) and C(6) stereogenic centres of the cycohexane ring. The conversion of β-amino ester 1,2-*syn*-1,6-*syn*-**34** into the corresponding 1,2-*anti*-1,6-*anti* diastereoisomer upon base-catalysed epimerisation of the C(1)-stereocentre was next investigated. However, treatment of **34** with KO^{t}Bu at rt returned only starting material. Even under more forcing conditions (10 equiv of base at reflux for several days), no trace of epimerisation was observed. Treatment of **34** with NaH followed by CD_3OD returned only starting material (i.e., no trace of D incorporation), suggesting that deprotonation was not occurring. This may be due to the favoured solution-phase conformation of **34** placing the α-C–H σ-bond coplanar with the carbonyl bond, which necessarily orientates the relevant orbital systems orthogonal. This conformation is displayed within the X-ray crystal structure of **34**, and these observations are consistent with the outcome of attempted epimerisation reactions in a related cyclopentane-derived system.[5g,h]

In order to verify that the stereochemical outcome observed in the mutual kinetic resolution of α,β-unsaturated esters **6**–**8** with lithium amide (*RS*)-**1** was identical to that observed upon substrate-directed addition of lithium *N*-benzyl-*N*-isopropylamide **13** to **6**–**8**, the configurations within β-amino esters **15** and **34** were correlated. Thus, hydrogenolysis of **15** (as an 85:15 mixture of **15**:[**16**+**17**]) mediated by Pearlman's catalyst gave *N*-isopropyl β-amino ester **37** in >95% de. Hydrogenolysis of **34** in a MeOH/acetone mixture promoted concomitant N-debenzylation and reductive amination to give **37** in >95% de (Scheme 7).



15, >95% de

37, >95% de
78% from **15**
94% from **34**

34, >95% de

Scheme 7. Reagents and conditions: (i) H_2 (1 atm), $Pd(OH)_2/C$, MeOH, rt, 24 h; (ii) H_2 (1 atm), $Pd(OH)_2/C$, MeOH/acetone (9:1), rt, 24 h.

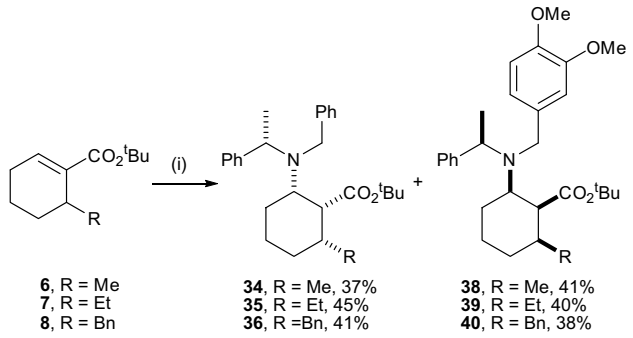
The results of these mutual kinetic resolutions demonstrate that excellent levels of enantiorecognition are shown between cyclic α,β-unsaturated esters **6**–**8** and lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **1** (*E* >40 in each case),[9] implying that their kinetic or parallel kinetic resolution via this conjugate addition protocol may be achieved. Although the development of an efficient kinetic resolution protocol would allow for the preparation of homochiral 6-substituted cishexacin derivatives, the experimental conditions for such a procedure must be carefully controlled, and may vary from substrate to substrate, in order that the reaction is stopped at ca. 50% conversion. Subsequent studies therefore focused on the development of a more robust parallel kinetic resolution protocol, employing a pseudoenantiomeric mixture of lithium amides, which has the advantage of negating the detrimental effects of mass action and, thus, potentially allowing a more facile experimental protocol.

2.4. Parallel kinetic resolution

In order to effect parallel kinetic resolution, α,β-unsaturated esters **6**–**8** were treated with a 50:50 mixture of lithium (*S*)-*N*-ben-

zyl-*N*-(α-methylbenzyl)amide (*S*)-**1** (2 equiv) and lithium (*R*)-*N*-3,4-dimethoxybenzyl-*N*-(α-methylbenzyl)amide (*R*)-**2** (2 equiv) in THF at −78 °C, followed by quenching with satd aq NH_4Cl, to give, in each case, a 50:50 mixture of two diastereoisomeric products **34**–**36** and **38**–**40** (derived from conjugate addition of (*S*)-**1** and (*R*)-**2**, respectively)[13] in >95% de, consistent with the complementary selectivities of the two pseudoenantiomeric lithium amides, with *E* >40.[9] In each case, the diastereoisomeric β-amino ester products were easily separated by flash column chromatography due to the disparate polarities of the *N*-benzyl and *N*-3,4-dimethoxybenzyl groups. β-Amino esters **34**–**36** were spectroscopically identical to the products of mutual kinetic resolution of α,β-unsaturated esters **6**–**8** with lithium (*RS*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **1**. The relative all-*syn* configuration around the cyclohexane ring within **38**–**40** was assigned on the basis of ^3J ^{1}H NMR coupling constant analyses, and the absolute configuration at C(2) was assigned, in each case, by reference to the transition state mnemonic developed to rationalise the very high facial bias of this class of lithium amides,[7] and by analogy to the X-ray crystal structure of **34** (Scheme 8).

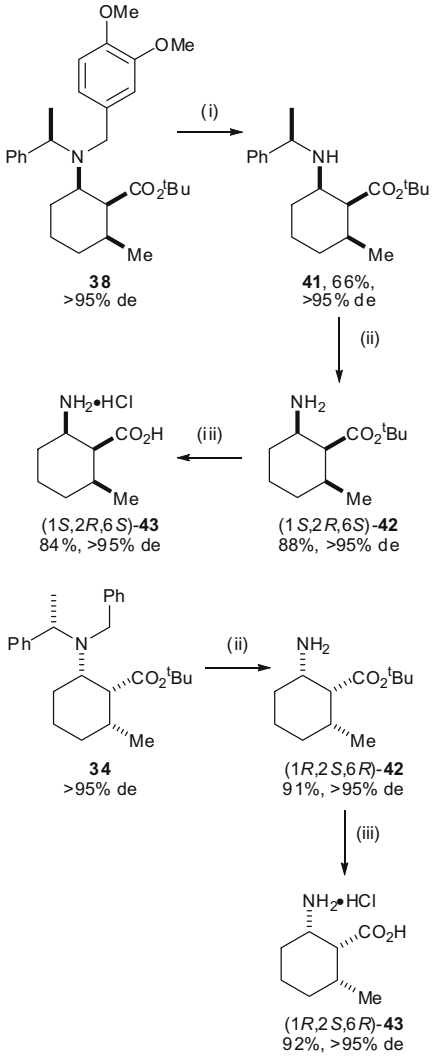
2.5. N-Deprotection: synthesis of 6-substituted cishexacin



Scheme 8. Reagents and conditions: (i) lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **1** (2 equiv), lithium (*R*)-*N*-3,4-dimethoxybenzyl-*N*-(α-methylbenzyl)amide (*R*)-**2** (2 equiv), THF, −78 °C, 3 h, then NH_4Cl (satd, aq). All compounds were isolated in > 95% de.

derivatives

In order to demonstrate the utility of this methodology for the synthesis of substituted cishexacin derivatives, a representative series of deprotection steps to give the free amino acid was undertaken with 6-methyl-substituted β-amino esters **34** and **38**. Hydrogenolysis of homochiral **34**, resulting from conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **1** in the parallel kinetic resolution protocol, furnished primary β-amino ester (1*R*,2*S*,6*R*)-**42** in >95% de, consistent with our previous reports that hydrogenolysis of *N*-benzyl-*N*-α-methylbenzyl protected β-amino esters proceeds with no loss of stereochemical integrity.[14] Meanwhile, treatment of homochiral β-amino ester **38** (from conjugate addition of lithium (*R*)-*N*-3,4-dimethyoxybenzyl-*N*-(α-methylbenzyl)amide **2**) with DDQ to effect oxidative cleavage of the *N*-3,4-dimethoxybenzyl group was followed by hydrogenolytic removal of the *N*-α-methylbenzyl group to give the enantiomeric primary β-amino ester (1*S*,2*R*,6*S*)-**42** in >95% de {for (1*R*,2*S*,6*R*)-**42**, $[\alpha]_D^{25} = -3.7$ (*c* 1.0 in $CHCl_3$); for (1*S*,2*R*,6*S*)-**42**, $[\alpha]_D^{25} = +1.2$ (*c* 1.0 in $CHCl_3$)}. Subsequent ester hydrolysis upon treatment with TFA gave the corresponding β-amino acids in >95% de in each case, which were isolated as the hydrochloride salts (1*R*,2*S*,6*R*)-**43** and (1*S*,2*R*,6*S*)-**43** due to their increased solubility {for (1*R*,2*S*,6*R*)-**43**, $[\alpha]_D^{25} = -2.0$ (*c* 1.0 in 1 M HCl); for (1*S*,2*R*,6*S*)-**43**, $[\alpha]_D^{25} = +1.8$ (*c* 1.0 in 1 M HCl)} (Scheme 9).



Scheme 9. Reagents and conditions: (i) DDQ, DCM/H_2O (5:1), rt, 48 h; (ii) H_2 (1 atm), $Pd(OH)_2$/C, MeOH, rt, 24 h; (iii) TFA/DCM (1:1), rt, 16 h then HCl, Et_2O.

3. Conclusion

tert-Butyl (*RS*)-6-alkyl-cyclohex-1-ene-carboxylates that possess a 6-alkyl substituent which is not α-branched display excellent levels of enantiorecognition in mutual kinetic resolutions with lithium (*RS*)-*N*-benzyl-*N*-(α-methylbenzyl)amide. Parallel kinetic resolution of *tert*-butyl 6-*n*-alkyl-cyclohexene-1-carboxylates using a pseudoenantiomeric mixture of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide and lithium (*R*)-*N*-3,4-dimethoxybenzyl-*N*-(α-methylbenzyl)amide furnishes the corresponding pseudoenantiomeric *tert*-butyl 2-amino-6-*n*-alkyl-cyclohexane-carboxylates, which are easily separable by chromatography. Subsequent N-deprotection followed by ester hydrolysis affords the enantiomeric (1*R*,2*S*,6*R*)- and (1*S*,2*R*,6*S*)-6-methyl-cishexacin derivatives in high diastereoisomeric purity.

4. Experimental

4.1. General experimental

All reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen or argon atmosphere using standard vacuum line techniques and glassware

that was flame dried and cooled under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.[15] Water was purified by an Elix® UV-10 system. All other solvents and reagents were used as supplied (analytical or HPLC grade) without prior purification. Organic layers were dried over $MgSO_4$. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm), iodine, 1% aq $KMnO_4$, or 10% ethanolic phosphomolybdic acid. Flash column chromatography was performed on Kieselgel 60 silica on a glass column, or on a Biotage SP4 flash column chromatography platform. Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter with a water-jacketed 10 cm cell. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g/100 mL. IR spectra were recorded on Bruker Tensor 27 FT-IR spectrometer as either a thin film on NaCl plates (film) or a KBr disc (KBr), as stated. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded on Bruker Avance spectrometers in the deuterated solvent stated. The field was locked by external referencing to the relevant deuteron resonance. Chemical shifts (δ) are reported in ppm and coupling constants (J) in Hz. Low-resolution mass spectra were recorded on either a VG MassLab 20-250 or a Micromass Platform 1 spectrometer. Accurate mass measurements were run on either a Bruker MicroTOF internally calibrated with polyalanine, or a Micromass GCT instrument fitted with a Scientific Glass Instruments BPX5 column (15 m × 0.25 mm) using amyl acetate as a lock mass.

4.2. General procedure 1: Grignard addition to *tert*-butyl (*RS*)-6-acetoxy-cyclohex-1-ene-carboxylate 5

CuI (0.05 equiv) was added in one portion to a solution of **5** (1 equiv) in THF (0.4 M) at −78 °C. After 5 min the appropriate Grignard reagent (1.5 equiv) was added dropwise and the mixture allowed to warm to rt over 1 h. The reaction was quenched with satd aq NH_4Cl, the layers were separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried and concentrated in vacuo. Purification via flash column chromatography gave the desired product.

4.3. General procedure 2: lithium amide conjugate addition to α,β-unsaturated esters

BuLi (3.95 equiv) was added dropwise to a stirred solution of the requisite amine(s) (4 equiv) in THF at −78 °C. After 30 min, a solution of the requisite α,β-unsaturated ester (1 equiv) in THF (overall concentration of α,β-unsaturated ester = 0.1 M) at −78 °C was added via cannula and the reaction mixture was stirred for a further 3 h before the addition of satd aq NH_4Cl solution. The organic layer was separated and the aqueous layer was extracted three times with Et_2O. The combined organic layers were washed sequentially with 10% aq citric acid, satd aq $NaHCO_3$ and brine, before being dried and concentrated in vacuo. Purification via flash column chromatography gave the desired product.

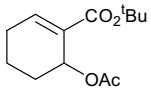
4.4. General procedure 3: hydrogenolysis of *N*-benzyl protected β-amino esters

$Pd(OH)_2/C$ (50% w/w to substrate) was added to a vigorously stirred solution of the requisite *N*-benzyl protected β-amino ester in degassed MeOH (0.1 M) at rt under argon. H_2 was bubbled through the solution and the atmosphere of the reaction vessel was saturated with H_2 (1 atm). After 24 h, the reaction mixture was filtered through Celite® (eluent MeOH) and concentrated in vacuo. The crude mixture was dissolved in Et_2O and washed sequentially with satd aq $NaHCO_3$ and brine, dried and concentrated in vacuo to give the desired product.

4.5. General procedure 4: hydrolysis of β-amino esters

TFA was added dropwise to the requisite β-amino ester in DCM at 0 °C (TFA/DCM, 1:1). The solution was vigorously stirred for 16 h at rt then concentrated in vacuo. HCl (2 M in Et_2O) and MeOH were added to the crude reaction mixture which was then stirred for 30 min and concentrated in vacuo. The residue was partitioned between Et_2O and H_2O, the layers were separated and the aqueous layer was concentrated to a volume of ~0.5 mL. Purification via ion-exchange chromatography (Dowex® 50WX8-200 resin, eluent 1 M aq NH_4OH) gave the free β-amino acid. Addition of HCl (2 M in Et_2O) and concentration in vacuo gave the β-amino acid hydrochloride salt.

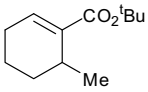
4.6. *tert*-Butyl (*RS*)-6-acetoxy-cyclohex-1-ene-carboxylate 5



tert-Butyl diethylphosphonoacetate (41.8 g, 166 mmol) was added in one portion to a vigorously stirred biphasic system of 50% aq glutaraldehyde (30.0 mL, 166 mmol), 7 M aq K_2CO_3 (47.0 mL, 332 mmol) and Aliquat® 336 (100 mL) in DCM (100 mL) at rt. After 72 h the mixture was filtered through Celite® (eluent DCM), the layers were separated and the organic layer was washed with brine (100 mL), dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, eluent 30–40 °C petrol/Et_2O, 19:1, increased to 30–40 °C petrol/Et_2O, 9:1) gave **3** as a viscous orange oil (contaminated with Aliquat® 336), which was used without further purification. Further elution gave di-*tert*-butyl nona-2,7-dieneoate **4** as a white solid (2.3 g, 5%);[16] δ_H (400 MHz, $CDCl_3$) 1.47 (9H, s, CMe_3), 1.60 (2H, quintet, J 7.4, C(5)H_2), 2.19 (4H, app qd, J 7.4, 1.4, C(4)H_2, C(6)H_2) 5,74 (2H, d, J 15.6, C(2)H, C(8)H), 6.81 (2H, dt, J 15.6, 7.4, C(3)H, C(5)H).

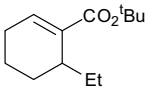
Ac_2O (27.7 mL, 293 mmol) was added dropwise to a stirred solution of **3** (11.6 g, ~58.6 mmol), Et_3N (8.9 mL, 87.9 mmol) and DMAP (30 mg) in DCM (30 mL) at rt. After 16 h the mixture was diluted with DCM (50 mL), washed sequentially with satd aq $NaHCO_3$ (2 × 50 mL) and brine (50 mL), dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 9:1) gave **5** as a colourless oil (6.3 g, 16% from glutaraldehyde over 2 steps); ν_{max} (film) 2977 (C–H), 1738 (C=O), 1714 (C=O), 1369, 1167, 929; δ_H (400 MHz, $CDCl_3$) 1.45 (9H, s, CMe_3), 1.60–1.66 (3H, m, C(4)H_2, C(5)H_A), 1.91–1.96 (1H, m, C(5)H_B), 2.03 (3H, s, COMe), 2.07–2.18 (1H, m, C(3)H_A), 2.29–2.38 (1H, m, C(3)H_B), 5.70 (1H, app br s, C(6)H), 7.18 (1H, dd, J 5.0, 2.8, C(2)H); δ_C (100 MHz, $CDCl_3$) 16.6 (C(4)), 21.3 (COMe), 25.7 (C(3)), 28.0 (CMe_3), 28.1 (C(5)), 64.8 (C(6)), 80.5 (CMe_3), 130.2 (C(1)), 144.4 (C(2)), 165.1 ($CO_2{}^t$Bu), 170.1 (COMe); m/z (ESI$^+$) 503 ([2M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{20}NaO_4{}^+$ ([M+Na]$^+$) requires 263.1254; found 263.1252.

4.7. *tert*-Butyl (*RS*)-6-methyl-cyclohex-1-ene-carboxylate 6



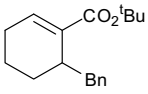
Following *General Procedure* 1, **5** (1.0 g, 4.16 mmol), CuI (21 mg, 0.11 mmol) and methylmagnesium chloride (2.3 M in THF, 2.7 mL, 6.21 mmol) in THF (10 mL) gave, after purification via flash column chromatography (gradient elution, eluent 30–40 °C petrol/Et_2O, 49:1, increased to 30–40 °C petrol/Et_2O, 24:1), **6** as a colourless oil (680 mg, 76%); ν_{max} (film) 2933, 2871, 1706 (C=O), 1644, 1455, 1366, 1170; δ_H (400 MHz, $CDCl_3$) 1.06 (3H, d, *J* 6.8, C(6)*Me*), 1.48 (9H, s, *J* 7.1, C*Me*$_3$), 1.45–1.69 (4H, m, C(4)H_2, C(5)H_2), 2.01–2.21 (2H, m, C(3)H_2), 2.50–2.66 (1H, m, C(6)*H*), 6.80 (1H, app t, *J* 4.0, C(2)*H*); δ_C (100 MHz, $CDCl_3$) 17.4 (*C*(4)), 20.2 (C(6)*Me*), 25.9 (*C*(3)), 27.8 (*C*(6)), 28.1 (C*Me*$_3$), 29.7 (*C*(5)), 79.8 (*C*Me$_3$), 136.9 (*C*(1)), 138.0 (*C*(2)), 167.0 (CO_2 ^{t}Bu); HRMS (FI$^+$) $C_{12}H_{20}O_2^+$ ([M]$^+$) requires 196.1458; found 196.1461.

4.8. *tert*-Butyl (*RS*)-6-ethyl-cyclohex-1-ene-carboxylate 7



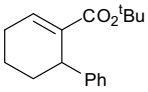
Following *General Procedure* 1, **5** (500 mg, 2.08 mmol), CuI (9.9 mg, 0.052 mmol) and ethylmagnesium chloride (2.0 M in THF, 1.6 mL, 3.2 mmol) in THF (5 mL) gave, after purification via flash column chromatography (gradient elution, eluent 30–40 °C petrol/Et_2O, 49:1, increased to 30–40 °C petrol/Et_2O, 24:1), **7** as a colourless oil (380 mg, 87%); ν_{max} (film) 3004, 2964, 1706 (C=O), 1640; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 8.0, C(6)CH_2*Me*), 1.22–1.24 (1H, m, C(6)CH_AH$_B$Me), 1.47 (9H, s, C*Me*$_3$), 1.54–1.57 (4H, m, C(4)H_A, C(5)H_2, C(6)CH$_A$$H_B$Me), 1.68–1.72 (1H, m, C(4)H_B), 2.09–2.13 (2H, m, C(3)H_2), 2.38–2.40 (1H, m, C(6)*H*), 6.80 (1H, app t, *J* 4.0, C(2)*H*); δ_C (100 MHz, $CDCl_3$) 12.3 (C(6)CH_2*Me*), 17.3 (*C*(5)), 25.0 (*C*(4)), 25.8 (*C*(3)), 26.4 (C(6)*C*H$_2$Me), 28.1 (C*Me*$_3$), 34.4 (*C*(6)), 79.7 (*C*Me$_3$), 136.4 (*C*(1)), 138.0 (*C*(2)), 167.1 (CO_2^{t}Bu); HRMS (FI$^+$) $C_{13}H_{22}O_2^+$ ([M]$^+$) requires 210.1614; found 210.1622.

4.9. *tert*-Butyl (*RS*)-6-benzyl-cyclohex-1-ene-1-carboxylate 8



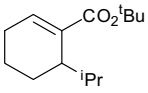
Following *General Procedure* 1, **5** (1.0 g, 4.16 mmol), CuI (21 mg, 0.11 mmol) and benzylmagnesium chloride (2 M in THF, 3.1 mL, 6.24 mmol) in THF (10 mL) gave, after purification via flash column chromatography (gradient elution, eluent 30–40 °C petrol/Et_2O, 49:1, increased to 30–40 °C petrol/Et_2O, 24:1), **8** as a colourless oil (972 mg, 86%); ν_{max} (film) 3003, 2976, 1702 (C=O), 1366, 1249; δ_H (400 MHz, $CDCl_3$) 1.35–1.38 (1H, m, C(5)H_A), 1.56 (9H, s, C*Me*$_3$), 1.58–1.69 (3H, m, C(4)H_2, C(5)H_B), 2.15–2.29 (2H, m, C(3)H_2), 2.39 (1H, dd, *J* 13.1, 7.8, C(6)CH_AH$_B$Ph), 2.84–2.86 (1H, m, C(6)*H*), 3.02 (1H, dd, *J* 13.1, 3.8, C(6)CH$_A$$H_B$Ph), 6.93 (1H, app t, *J* 3.8, C(2)*H*), 7.15–7.33 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.8 (*C*(4)), 24.3 (*C*(5)), 25.9 (*C*(3)), 28.2 (C*Me*$_3$), 35.0 (*C*(6)), 39.5 (C(6)CH_2Ph), 80.0 (*C*Me$_3$), 125.8 (*p-Ph*), 128.2, 128.3 (*o-Ph*, *m-Ph*), 135.5 (*C*(1)), 139.2 (*C*(2)), 141.3 (*i-Ph*), 166.7 (CO_2^{t}Bu); HRMS (FI$^+$) $C_{18}H_{24}O_2^+$ ([M]$^+$) requires 272.1771; found 272.1775.

4.10. *tert*-Butyl (*RS*)-6-phenyl-cyclohex-1-ene-carboxylate 9



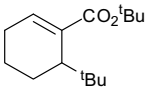
Following *General Procedure* 1, **5** (200 mg, 0.83 mmol), CuI (8 mg, 0.04 mmol) and phenylmagnesium chloride (2 M in THF, 0.62 mL, 1.25 mmol) in THF (0.5 mL) gave, after purification via flash column chromatography (gradient elution, eluent 30–40 °C petrol/Et_2O, 49:1, increased to 30–40 °C petrol/Et_2O, 24:1), **9** as a colourless oil (173 mg, 80%); ν_{max} (film) 2933, 1710 (C=O), 1367, 1254, 1168; δ_H (400 MHz, $CDCl_3$) 1.23 (9H, s, C*Me*$_3$), 1.50–1.59 (2H, m, C(4)H_2), 1.68–1.75 (1H, m, C(5)H_A), 1.91–2.00 (1H, m, C(5)H_B), 2.18–2.37 (2H, m, C(3)H_2), 3.83 (1H, app br s, C(6)*H*), 7.13–7.20 (4H, m, C(2)*H*, *Ph*), 7.27 (2H, app t, *J* 7.5, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.8 (*C*(4)), 25.9 (*C*(3)), 27.8 (C*Me*$_3$), 31.8 (*C*(5)), 40.3 (*C*(6)), 79.9 (*C*Me$_3$), 125.7 (*p-Ph*), 127.7, 128.0 (*o-Ph*, *m-Ph*), 133.8 (*C*(1)), 140.1 (*C*(2)), 145.8 (*i-Ph*), 166.6 (CO_2^{t}Bu); *m/z* (ESI$^+$) 534 ([2M+NH_4]$^+$, 100%); HRMS (ESI$^+$) $C_{17}H_{22}NaO_4^+$ ([M+Na]$^+$) requires 281.1512; found 281.1510.

4.11. *tert*-Butyl (*RS*)-6-isopropyl-cyclohex-1-ene-carboxylate 10



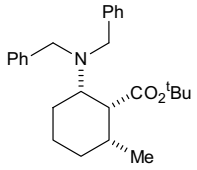
Following *General Procedure* 1, **5** (200 mg, 0.22 mmol), CuI (8 mg, 0.04 mmol) and isopropylmagnesium chloride (2 M in THF, 0.62 mL, 1.25 mmol) in THF (0.5 mL) gave, after purification via flash column chromatography (gradient elution, eluent 30–40 °C petrol/Et_2O, 49:1, increased to 30–40 °C petrol/Et_2O, 24:1), **10** as a colourless oil (130 mg, 70%); ν_{max} (film) 2961, 1708 (C=O), 1367, 1171, 1071; δ_H (400 MHz, $CDCl_3$) 0.83 (3H, d, *J* 6.8, *Me*CHMe), 0.90 (3H, d, *J* 6.8, MeCH*Me*), 1.48 (9H, s, C*Me*$_3$), 1.48–1.54 (2H, m, C(4)H_A, C(5)H_A), 1.61–1.70 (2H, m, C(4)H_B, C(5)H_B), 1.90 (1H, app septet, *J* 6.8 C*H*Me$_2$), 2.09–2.14 (2H, m, C(3)H_2), 2.42–2.48 (1H, m, C(6)*H*), 6.76 (1H, app t, *J* 3.8, C(2)*H*); δ_C (100 MHz, $CDCl_3$) 18.7 (*C*(4)), 19.2, 21.0 (CH*Me*$_2$), 23.3 (*C*(5)), 25.6 (*C*(3)), 28.1 (C*Me*$_3$), 30.5 (*C*HMe$_2$), 38.6 (*C*(6)), 79.7 (*C*Me$_3$), 136.4 (*C*(1)), 137.9 (*C*(2)), 168.1 (CO_2^{t}Bu); HRMS (FI$^+$) $C_{14}H_{24}O_2^+$ ([M]$^+$) requires 224.1771; found 224.1779.

4.12. *tert*-Butyl (*RS*)-6-*tert*-butyl-cyclohex-1-ene-carboxylate 11



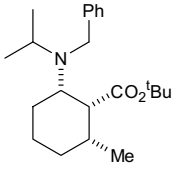
Following *General Procedure* 1, **5** (200 mg, 0.83 mmol), CuI (8 mg, 0.04 mmol) and *tert*-butylmagnesium chloride (2 M in THF, 0.62 mL, 1.25 mmol) in THF (0.5 mL) gave, after purification via flash column chromatography (gradient elution, eluent 30–40 °C petrol/Et_2O, 49:1, increased to 30–40 °C petrol/Et_2O, 24:1), **11** as a colourless oil (164 mg, 83%); ν_{max} (film) 2967, 1710 (C=O), 1366, 1251, 1169; δ_H (400 MHz, $CDCl_3$) 0.91 (9H, s, C(6)C*Me*$_3$), 1.45–1.57 (2H, m, C(4)H_A, C(5)H_A), 1.48 (9H, s, OC*Me*$_3$), 1.70–1.79 (1H, m, C(4)H_B), 1.80–1.88 (1H, m, C(5)H_B), 2.08–2.14 (2H, m, C(3)H_2), 2.59–2.64 (1H, m, C(6)*H*), 6.70 (1H, app t, *J* 4.2, C(2)*H*); δ_C (100 MHz, $CDCl_3$) 19.5 (*C*(4)), 24.2 (*C*(5)), 24.7 (*C*(3)), 28.0 (OC*Me*$_3$), 29.1 (C(6)C*Me*$_3$), 35.6 (C(6)*C*Me$_3$), 41.2 (*C*(6)), 79.7 (OCMe$_3$), 135.7 (*C*(1)), 138.1 (*C*(2)), 169.8 (CO_2^{t}Bu); HRMS (FI$^+$) $C_{15}H_{26}O_2^+$ ([M]$^+$) requires 238.1927; found 238.1934.

4.13. *tert*-Butyl (1*RS*,2*SR*,6*RS*)-2-*N*,*N*-dibenzylamino-6-methylcyclohexane-carboxylate 14



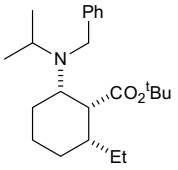
Following *General Procedure* 2, BuLi (2.2 M in hexanes, 0.46 mL, 1.00 mmol), dibenzylamine (201 mg, 1.02 mmol) in THF (2 mL) and **6** (50 mg, 0.26 mmol) in THF (0.6 mL) gave a 95:3:2 mixture of **14**:**16**:**17**. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 9:1) gave **14** as a colourless oil (80 mg, 80%, >95% de); ν_{max} (film) 3027, 2930, 1718 (C=O), 1454, 1149, 966; δ_H (400 MHz, $CDCl_3$) 0.93 (3H, d, *J* 6.8, C(6)*Me*) 1.27–1.33 (2H, m, C(4)H_A, C(5)H_A), 1.47 (9H, s, CMe_3), 1.50–1.54 (1H, m, C(6)*H*), 1.64–1.70 (2H, m, C(3)H_A, C(5)H_B), 1.82–1.89 (1H, m, C(4)H_B), 2.13–2.19 (1H, m, C(3)H_B), 2.70 (1H, app dt, *J* 12.5, 4.4, C(2)*H*), 2.87 (1H, app t, *J* 4.4, C(1)*H*), 3.72 (4H, app s, N(CH_2Ph)$_2$), 7.21 (2H, t, *J* 7.2, *Ph*), 7.30 (4H, app t, *J* 7.2, *Ph*), 7.40 (4H, d, *J* 7.2, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.3 (C(6)*Me*), 23.1 (*C*(3)), 25.7 (*C*(4)), 28.1 (CMe_3), 28.8 (*C*(5)), 35.2 (*C*(6)), 49.7 (*C*(1)), 54.5 (N(CH_2Ph)$_2$), 60.8 (*C*(2)), 80.3 (*C*Me$_3$), 126.6 (*p-Ph*), 128.1, 128.4 (*o-Ph*, *m-Ph*), 140.8 (*i-Ph*), 174.1 (*C*O$_2$^{t}Bu); *m*/*z* (ESI$^+$) 394 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{36}NO_2^+$ ([M+H]$^+$) requires 394.2741; found 394.2740. Data for *syn*-**16**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 3.04–3.09 (1H, m, C(1)*H*), 5.71–5.74 (1H, m, C(3)*H*), 5.81–5.84 (1H, m, C(2)*H*). Data for *anti*-**17**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 3.04–3.09 (1H, m, C(1)*H*), 5.68–5.70 (1H, m, C(3)*H*), 5.84–5.87 (1H, m, C(2)*H*).

4.14. *tert*-Butyl (1*RS*,2*SR*,6*RS*)-2-[*N*-benzyl-*N*-isopropylamino]-6-methyl-cyclohexane-carboxylate 15



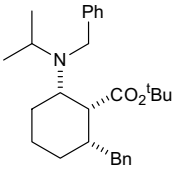
Following *General Procedure* 2, BuLi (2.2 M in hexanes, 0.46 mL, 1.00 mmol), *N*-benzyl-*N*-isopropylamine (152 mg, 1.02 mmol) in THF (2 mL) and **6** (50 mg, 0.26 mmol) in THF (0.6 mL) gave an 85:9:6 mixture of **15**:**16**:**17**. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 9:1) gave an 85:9:6 mixture of **15**:**16**:**17** colourless oil (74 mg, **15** in >95% de); ν_{max} (film) 2960, 1718 (C=O), 1455, 1366, 1147. Data for **15**: δ_H (400 MHz, $CDCl_3$) 0.94 (3H, d, *J* 6.6, C(6)*Me*), 0.97 (3H, d, *J* 6.6, *Me*CHMe), 1.03 (3H, d, *J* 6.6, MeCH*Me*), 1.28–1.35 (2H, m, C(4)H_A, C(5)H_A), 1.40 (9H, s, CMe_3), 1.50–1.68 (3H, m, C(3)H_A, C(5)H_B, C(6)*H*), 1.79–1.85 (1H, m, C(4)H_B), 2.03–2.09 (1H, m, C(3)H_B), 2.72 (1H, app t, *J* 4.3, C(1)*H*), 2.77 (1H, app dt, *J* 12.5, 4.3, C(2)*H*), 3.08 (1H, septet, *J* 6.6, C*H*Me$_2$), 3.76 (2H, ABq, J_{AB} 15.5, NCH_2Ph), 7.18 (1H, app t, *J* 7.4, *Ph*), 7.27 (2H, app t, *J* 7.4, *Ph*), 7.39 (2H, app d, *J* 7.4, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.0 (*Me*CHMe), 19.6 (*C*(6)*Me*), 20.2 (MeCH*Me*), 25.3 (*C*(3)), 25.9 (*C*(4)), 28.1 (CMe_3), 28.6 (*C*(5)), 35.2 (*C*(6)), 48.5 (*C*HMe$_2$), 50.5 (NCH_2), 53.5 (*C*(1)), 59.3 (*C*(2)), 80.0 (*C*Me$_3$), 126.0 (*p-Ph*), 127.7, 127.8 (*o-Ph*, *m-Ph*), 143.0 (*i-Ph*), 173.8 (*C*O$_2$^{t}Bu); *m*/*z* (ESI$^+$) 346 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{36}NO_2^+$ ([M+H]$^+$) 346.2741; found 346.2745.

4.15. *tert*-Butyl (1*RS*,2*SR*,6*RS*)-2-[*N*-benzyl-*N*-isopropylamino]-6-ethyl-cyclohexane-carboxylate 18



Following *General Procedure* 2, BuLi (2.3 M in hexanes, 1.21 mL, 2.80 mmol), *N*-benzyl-*N*-isopropylamine (420 mg, 2.84 mmol) in THF (5 mL) and **7** (150 mg, 0.71 mmol) in THF (2 mL) gave a 94:5:1 mixture of **18**:**20**:**21**. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 49:1) gave **18** as a colourless oil (196 mg, 77%, >95% de); ν_{max} (film) 3084, 2962, 2861, 1717 (C=O), 1455, 1328, 1145; δ_H (400 MHz, $CDCl_3$) 0.95 (3H, d, *J* 6.5, C(6)CH$_2$*Me*), 0.98 (3H, d, *J* 6.6, *Me*CHMe), 1.04 (3H, d, *J* 6.6, MeCH*Me*), 1.19-1.35 (4H, m, C(4)H_A, C(5)H_A, C(6)CH_2Me), 1.39 (9H, s, CMe_3), 1.41–1.44 (1H, m, C(6)*H*), 1.53–1.59 (2H, m, C(3)H_A, C(5)H_B), 1.81–1.88 (1H, m, C(4)H_B), 2.08–2.12 (1H, m, C(3)H_B), 2.76 (1H, app dt, *J* 12.5, 4.3, C(2)*H*), 2.81 (1H, t, *J* 4.3, C(1)*H*), 3.07 (1H, app septet, *J* 6.6, C*H*Me$_2$), 3.76 (2H, ABq, J_{AB} 15.6, NCH_2Ph), 7.16–7.41 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.0 (C(6)CH$_2$*Me*), 18.0, 20.3 (CH*Me*$_2$), 25.7, 25.9 (*C*(3), *C*(4)), 26.6, 27.0 (*C*(5), C(6)CH$_2$Me), 28.1 (CMe_3), 42.8 (*C*(6)), 48.5 (*C*HMe$_2$), 50.5 (NCH_2Ph), 51.4 (*C*(1)), 59.3 (*C*(2)), 79.9 (*C*Me$_3$), 126.0 (*p-Ph*), 127.2, 128.7 (*o-Ph*, *m-Ph*), 142.9 (*i-Ph*), 173.8 (*C*O$_2$^{t}Bu); *m*/*z* (ESI$^+$) 360 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{38}NO_2^+$ ([M+H]$^+$) requires 360.2897; found 360.2896. Data for *syn*-**20**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 3.08–3.12 (1H, m, C(1)*H*), 5.70–5.73 (1H, m, C(3)*H*), 5.83–5.86 (1H, m, C(2)*H*). Data for *anti*-**21**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 3.08–3.12 (1H, m, C(1)*H*), 5.67–5.70 (1H, m, C(3)*H*), 5.86–5.89 (1H, m, C(2)*H*).

4.16. *tert*-Butyl (1*RS*,2*SR*,6*SR*)-2-[*N*-benzyl-*N*-isopropylamino]-6-benzyl-cyclohexane-1-carboxylate 19



Following *General Procedure* 2, BuLi (2.3 M in hexanes, 0.94 mL, 2.17 mmol), *N*-benzyl-*N*-isopropylamine **13** (327 mg, 2.20 mmol) in THF (5 mL) and **8** (150 mg, 0.55 mmol) in THF (2 mL) gave an 89:10:1 mixture of **19**:**22**:**23**. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 49:1) gave **19** as a colourless oil (192 mg, 83%, >95% de); ν_{max} (film) 2932, 1716 (C=O), 1602, 1494, 1391, 1146; δ_H (400 MHz, $CDCl_3$) 0.98 (3H, d, *J* 6.6, *Me*CHMe), 1.02 (3H, d, *J* 6.6, MeCH*Me*), 1.16–1.19 (1H, m, C(4)H_A), 1.31–1.35 (1H, m, C(5)H_A), 1.46 (9H, s, CMe_3), 1.51–1.65 (2H, m, C(3)H_A, C(5)H_B), 1.65–1.83 (2H, m, C(4)H_B, C(6)*H*), 2.09–2.12 (1H, m, C(3)H_B), 2.37 (1H, dd, *J* 13.3, 9.4, C(6)C$H_A$$H_B$Ph), 2.77–2.80 (2H, m, C(2)*H*, C(6)CH$_A$$H_B$Ph), 2.88 (1H, app t, *J* 3.8, C(1)*H*), 3.07 (1H, app septet, *J* 6.6, C*H*Me$_2$), 3.75 (2H, ABq, J_{AB} 15.6, NCH_2Ph), 7.18–7.23 (4H, m, *Ph*), 7.26–7.32 (4H, m, *Ph*), 7.39–7.41 (2H, app d, *J* 7.3, *Ph*); δ_C (100 MHz, $CDCl_3$) δ_C (100 MHz, $CDCl_3$) 18.1, 20.2 (CH*Me*$_2$), 25.6, 25.8 (*C*(4), *C*(5)), 28.2 (CMe_3), 40.8 (C(6)CH$_2$Ph), 43.0 (*C*(6)), 48.5 (*C*HMe$_2$), 50.5 (NCH_2Ph$_2$), 52.3 (*C*(1)), 59.5 (*C*(2)), 80.3 (*C*Me$_3$), 125.9, 126.1 (*p-Ph*), 127.7, 127.9, 128.2, 129.1 (*o-Ph*, *m-Ph*), 140.9, 142.9 (*i-Ph*), 173.7 (*C*O$_2$^{t}Bu); *m*/*z* (ESI$^+$) 422 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{40}NO_2^+$ ([M+H]$^+$) requires 422.3054; found 422.3053. Data

for *syn*-**22**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 3.09–3.13 (1H, m, C(1)*H*), 5.75–5.78 (1H, m, C(3)*H*), 5.84–5.87 (1H, m, C(2)*H*). Data for *anti*-**23**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 3.09–3.13 (1H, m, C(1)*H*), 5.72–5.75 (1H, m, C(3)*H*), 5.87–5.90 (1H, m, C(2)*H*).

4.17. Addition of lithium *N*-benzyl-*N*-isopropylamide 13 to *tert*-butyl (*RS*)-6-phenyl-cyclohex-1-ene-carboxylate 9

Following *General Procedure* 2, BuLi (2.3 M in hexanes, 0.46 mL, 1.06 mmol), *N*-benzyl-*N*-isopropylamine (163 mg, 1.09 mmol) in THF (5 mL) and **9** (176 mg, 0.68 mmol) in THF (1.8 mL) gave a 78:13:9 mixture of **24**:**27**:**28**. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 49:1) gave a 78:13:9 mixture of **24**:**27**:**28** as a colourless oil (232 mg, **24** in >95% de). Data for **24**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 3.06–3.13 (2H, m, C(1)*H*, C*H*Me_2), 3.22–3.27 (1H, m, C(2)*H*), 3.95 (2H, ABq, J_{AB} 14.6, NCH_2Ph); δ_C (100 MHz, $CDCl_3$) [selected peaks] 49.4 (C*H*Me_2), 53.1 (*C*(2)), 53.9 (*C*(1)). Data for *syn*-**27**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 3.42–3.47 (1H, m, C(1)*H*), 5.95–5.98 (1H, m, C(3)*H*), 6.00–6.03 (1H, m, C(2)*H*); δ_C (100 MHz, $CDCl_3$) [selected peaks] 47.0 (*C*(1)), 124.7 (*C*(3)), 130.0 (*C*(2)). Data for *anti*-**28**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 3.42–3.47 (1H, m, C(1)*H*), 5.92–5.95 (1H, m, C(3)*H*), 6.03–6.06 (1H, m, C(2)*H*); δ_C (100 MHz, $CDCl_3$) [selected peaks] 47.0 (*C*(1)), 124.7 (*C*(3)), 130.0 (*C*(2)).

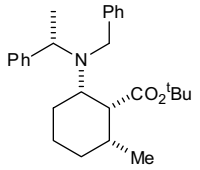
4.18. Addition of lithium *N*-benzyl-*N*-isopropylamide 13 to *tert*-butyl (*RS*)-6-isopropyl-cyclohex-1-ene-carboxylate 10

Following *General Procedure* 2, BuLi (2.3 M in hexanes, 0.38 mL, 0.87 mmol), *N*-benzyl-*N*-isopropylamine (133 mg, 0.89 mmol) in THF (1.5 mL) and **10** (50 mg, 0.22 mmol) in THF (0.7 mL) gave a 41:35:24 mixture of **25**:**29**:**30**. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 49:1) gave a 41:35:24 mixture of **25**:**29**:**30** as a colourless oil (64 mg, **25** in >95% de). Data for **25**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 2.73 (1H, app dt, *J* 12.5, 4.1, C(2)*H*), 2.94 (1H, app t, *J* 4.1, C(1)*H*), 3.05 (1H, app septet, *J* 6.6, C*H*Me_2), 3.74 (2H, ABq, J_{AB} 15.6, NCH_2Ph); δ_C (100 MHz, $CDCl_3$) [selected peaks] 49.9 (*C*(1)), 50.6 (N*C*H_2Ph), 59.7 (*C*(2)). Data for *syn*-**29** and *anti*-**30**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 3.10–3.16 (1H, m, C(1)*H*), 5.64–5.70 (1H, m, C(3)*H*), 5.86–5.92 (1H, m, C(2)*H*); δ_C (100 MHz, $CDCl_3$) [selected peaks] 44.3 (*C*(1)), 124.7 (*C*(3)), 130.4 (*C*(2)).

4.19. Addition of lithium *N*-benzyl-*N*-isopropylamide 13 to *tert*-butyl (*RS*)-6-*tert*-butyl-cyclohex-1-ene-carboxylate 11

Following *General Procedure* 2, BuLi (2.3 M in hexanes, 1.00 mL, 2.36 mmol), *N*-benzyl-*N*-isopropylamine **13** (361 mg, 2.42 mmol) in THF (4.5 mL) and **11** (144 mg, 0.61 mmol) in THF (1.6 mL) gave a 13:70:17 mixture of **26**:**31**:**32**. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 49:1) gave a 13:70:17 mixture of **26**:**31**:**32** as a colourless oil (146 mg, **26** in >95% de). Data for **26**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 3.07 (1H, app septet, *J* 6.6, C*H*Me_2), 3.60 (2H, ABq, J_{AB} 15.3, NCH_2Ph). Data for *syn*-**31**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 3.08–3.13 (1H, m, C(1)*H*), 5.60–5.66 (1H, m, C(3)*H*), 5.81–5.86 (1H, m, C(2)*H*); δ_C (100 MHz, $CDCl_3$) 18.9, 27.0 (*C*(4), *C*(5)), 28.0, 28.1 (C*Me*$_3$, C(6)C*Me*$_3$), 32.9 (*C*Me$_3$), 43.9 (*C*(6)), 48.0 (*C*(1)), 80.2 (*C*Me$_3$), 125.8 (*C*(3)), 130.3 (*C*(2)), 173.9 (*C*$O_2{}^t$Bu). Data for *anti*-**32**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 2.88–2.94 (1H, m, C(1)*H*), 5.46–5.51 (1H, m, C(3)*H*), 5.87–5.91 (1H, m, C(2)*H*); δ_C (100 MHz, $CDCl_3$) 22.8, 25.2 (*C*(4), *C*(5)), 27.8, 28.0 (C*Me*$_3$, C(6)C*Me*$_3$), 33.5 (*C*Me$_3$), 44.1 (*C*(6)), 46.1 (*C*(1)), 80.2 (*C*Me$_3$), 125.6 (*C*(3)), 130.2 (*C*(2)), 175.3 (*C*$O_2{}^t$Bu).

4.20. *tert*-Butyl (1*RS*,2*SR*,6*RS*,α*SR*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-6-methyl-cyclohexane-carboxylate 34



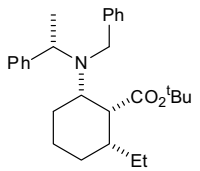
Following *General Procedure* 2, BuLi (2.3 M in hexanes, 4.45 mL, 10.3 mmol), (*RS*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (2.24 g, 10.6 mmol) in THF (22 mL) and **6** (519 mg, 2.65 mmol) in THF (4.5 mL) gave a 95:3:2 mixture of **34**:**16**:**17**. Purification via flash column chromatography (gradient elution, eluent 30–40 °C petrol/Et_2O, 49:1, increased to 30–40 °C petrol/Et_2O, 24:1) gave **34** as a white solid (923 mg, 85%, >95% de); mp 90–92 °C (DCM/pentane); ν_{max} (film) 2931, 1717 (C=O), 1453, 1367, 1150; δ_H (400 MHz, $CDCl_3$) 0.85 (3H, d, *J* 6.9, C(6)*Me*), 1.18–1.27 (2H, m, C(4)H_A, C(5)H_A), 1.32 (3H, d, *J* 6.8, C(α)*Me*), 1.38–1.42 (1H, m, C(6)*H*), 1.46 (9H, s, C*Me*$_3$), 1.52–1.66 (2H, m, C(3)H_A, C(5)H_B), 1.78–1.84 (1H, m, C(4)H_B), 2.09–2.19 (1H, m, C(3)H_B), 2.55 (1H, app t, *J* 4.4, C(1)*H*), 2.67–2.70 (1H, m, C(2)*H*), 3.82–3.95 (2H, ABq, J_{AB} 15.0, NCH_2Ph), 4.06 (1H, q, *J* 6.8, C(α)*H*), 7.19–7.25 (2H, m, *Ph*), 7.29–7.36 (4H, m, *Ph*), 7.45–7.57 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.4 (C(α)*Me*), 19.4 (C(6)*Me*), 25.5 (*C*(3)), 25.8 (*C*(4)), 28.2 (C*Me*$_3$), 28.6 (*C*(5)), 35.2 (*C*(6)), 51.0 (NCH_2), 52.0 (*C*(1)), 56.7 (*C*(α)), 59.7 (*C*(2)), 80.3 (*C*Me$_3$), 126.4, 126.5 (*p*-*Ph*), 127.8, 127.9, 128.0, 128.2 (*o*-*Ph*, *m*-*Ph*), 142.5, 144.6 (*i*-*Ph*), 174.1 (*C*$O_2{}^t$Bu); *m*/*z* (ESI$^+$) 408 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{28}NO_2{}^+$ ([M+H]$^+$) requires 408.2897; found 408.2903.

4.21. X-ray crystal structure determination for 34

Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite monochromated Mo-*K*α radiation using standard procedures at 190 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[17]

X-ray crystal structure data for **34** [$C_{27}H_{37}NO_2$]: M = 407.60, triclinic, space group $P\bar{1}$, a = 9.9898(1) Å, b = 10.4028(2) Å, c = 14.0324(2) Å, α = 107.8397(7), β = 92.5204(7)°, γ = 116.5274(8)°, V = 1213.70(3) Å^3, Z = 2, μ = 0.069 mm^{-1}, colourless plate, crystal dimensions = 0.1 × 0.1 × 0.2 mm^3. A total of 5514 unique reflections were measured for $5 < \theta < 27$ and 3618 reflections were used in the refinement. The final parameters were wR_2 = 0.047 and R_1 = 0.042 [$I > 3.0\sigma(I)$]. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 679351. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

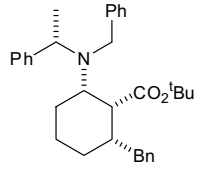
4.22. *tert*-Butyl (1*RS*,2*SR*,6*RS*,α*SR*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-6-ethyl-cyclohexane-carboxylate 35



Following *General Procedure* 2, BuLi (2.3 M in hexanes, 1.22 mL, 2.80 mmol), (*RS*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (639 mg, 2.84 mmol) in THF (5 mL) and **7** (150 mg, 0.71 mmol)

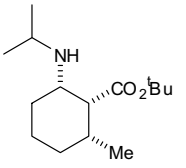
in THF (2 mL) gave a 95:3:2 mixture of **35**:**20**:**21**. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 99:1) gave **35** as a colourless oil (196 mg, 76%, >95% de); ν_{max} (film) 2968, 2933, 1714 (C=O), 1367, 1147; δ_H (400 MHz, $CDCl_3$) 0.83 (3H, t, *J* 7.3, CH_2Me), 1.02–1.10 (1H, m, C(6)*H*), 1.14–1.25 (3H, m, C(6)CH_2Me, C(4)H_A), 1.32 (3H, d, *J* 6.7, C(α)*Me*), 1.46 (9H, s, CMe_3), 1.48–1.65 (3H, m, C(3)H_A, C(5)H_2), 1.81–1.84 (1H, m, C(4)H_B), 2.14–2.21 (1H, m, C(3)H_B), 2.64–2.68 (2H, m, C(1)*H*, C(2)*H*), 3.87 (2H, ABq, J_{AB} 14.9, NCH_2), 4.06 (1H, q, *J* 6.7, C(α)*H*), 7.19–7.26 (2H, m, *Ph*), 7.30–7.35 (4H, m, *Ph*), 7.51–7.62 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 11.7 (CH_2Me), 15.4 (C(α)*Me*), 25.8 (*C*(5)), 25.9, 26.6, 26.7, (*C*(3), *C*(4), CH_2CH_3), 28.2 (CMe_3), 42.6 (*C*(6)), 49.5 (*C*(1)), 51.0 (NCH_2), 56.7 (*C*(α)), 59.7 (*C*(2)), 80.1 (*C*Me_3), 126.3, 126.5 (*p-Ph*), 127.8, 127.9, 128.0, 128.1 (*o-Ph*, *m-Ph*), 142.6, 144.5 (*i-Ph*), 174.1 ($CO_2{}^tBu$); *m*/*z* (CI^+) 422.4 ($[M+H]^+$, 100%); HRMS (CI^+) $C_{28}H_{40}NO_2{}^+$ ($[M+H]^+$) requires 422.3054; found 422.3054.

4.23. *tert*-Butyl (1*RS*,2*SR*,6*SR*,α*SR*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-6-benzyl-cyclohexane-carboxylate 36



Following *General Procedure* 2, BuLi (2.3 M in hexanes, 0.95 mL, 2.17 mmol), (*RS*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (495 mg, 2.20 mmol) in THF (5 mL) and **8** (150 mg, 0.55 mmol) in THF (2 mL) gave a 95:3:2 mixture of **36**:**22**:**23**. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 99:1) gave **36** as a pale yellow oil (223 mg, 84%, >95% de); ν_{max} (film) 2971, 2931, 1716 (C=O), 1493, 1206; δ_H (400 MHz, $CDCl_3$) 1.12–1.17 (1H, m, C(4)H_A), 1.29 (3H, d, *J* 6.6, C(α)*Me*), 1.43–1.47 (2H, m, C(5)H_A, C(6)*H*), 1.54 (9H, s, CMe_3), 1.55–1.65 (2H, C(5)H_B), 1.68–1.72 (1H, m, C(3)H_A), 1.79–1.83 (1H, m, C(4)H_B), 2.18 (1H, app qd, *J* 12.7, 3.8, C(3)H_B), 2.39 (1H, dd, *J* 13.4, 8.1, C(6)C$H_A$$H_B$Ph), 2.56 (1H, dd, *J* 13.4, 8.1, C(6)C$H_A$$H_B$Ph), 2.62 (1H, app t, *J* 4.0, C(1)*H*), 2.66–2.70 (1H, m, C(2)*H*), 3.90 (2H, ABq, J_{AB} 18.0, NCH_2Ph), 4.03 (1H, q, *J* 6.6, C(α)*H*), 7.10 (2H, d, *J* 7.1, *Ph*), 7.22–7.38 (11H, m, *Ph*), 7.51 (2H, d, *J* 7.1, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.1 (C(α)*Me*), 25.7, 25.9, 26.1 (*C*(3), *C*(4), *C*(5)), 28.5 (CMe_3), 37.5 (C(6)CH_2Ph), 42.8 (*C*(6)), 49.6 (*C*(1)), 51.1 (NCH_2Ph), 57.1 (*C*(α)), 60.5 (*C*(2)), 80.5 (*C*Me_3), 125.9, 126.4, 126.5 (*p-Ph*), 127.7, 128.0, 128.1, 129.0, 129.3 (*o-Ph*, *m-Ph*), 140.6, 142.7, 144.4 (*i-Ph*), 174.0 ($CO_2{}^tBu$); *m*/*z* (CI^+) 484 ($[M+H]^+$, 100%); HRMS (CI^+) $C_{33}H_{42}NO_2{}^+$ ($[M+H]^+$) requires 484.3210; found 484.3213.

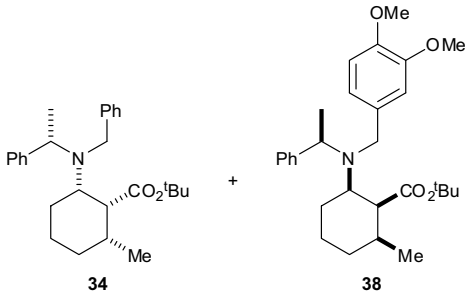
4.24. *tert*-Butyl (1*RS*,2*SR*,6*RS*)-2-[*N*-isopropylamino]-6-methyl-cyclohexane-1-carboxylate 37



From **15**: Following *General Procedure* 3, $Pd(OH)_2$/C (37 mg, 50% w/w of substrate) and **15** (74 mg, ~0.21 mmol) gave **37** a colourless oil (42 mg, 78%, >95% de); ν_{max} (film) 2930, 1722 (C=O), 1457, 1366, 1249; δ_H (400 MHz, $CDCl_3$) 0.94 (3H, d, *J* 6.6, C(6)*Me*), 0.97 (3H, d, *J* 6.6, *Me*CHMe), 1.03 (3H, d, *J* 6.6, MeCH*Me*), 1.29–1.39 (2H, m, C(4)H_A, C(5)H_A), 1.46 (9H, s, CMe_3), 1.55–1.62 (3H, m, C(3)H_A, C(5)H_B, C(6)*H*), 1.69–1.74 (1H, m, C(3)H_B), 1.77–1.82 (1H, m, C(4)H_B), 2.71 (1H, app dt, *J* 11.7, 4.5, C(2)*H*), 2.83 (1H, app t, *J* 4.5, C(1)*H*), 3.08 (1H, app septet, *J* 6.6, C*H*Me_2); δ_C (100 MHz, $CDCl_3$) 20.0 (*C*(6)*Me*), 22.2, 23.8 (CH*Me*$_2$), 25.1 (*C*(4)), 28.3 (CMe_3), 28.5, 28.6 (*C*(3), (*C*(5)), 34.1 (*C*(6)), 43.9 (*C*HMe$_2$), 50.5 (*C*(1)), 54.8 (*C*(2)), 80.0 (*C*Me$_3$), 172.6 ($CO_2{}^tBu$); *m*/*z* (ESI^+) 256 ($[M+H]^+$, 60%); HRMS (ESI^+) $C_{15}H_{30}NO_2{}^+$ ($[M+H]^+$) 356.2271; found 256.2278.

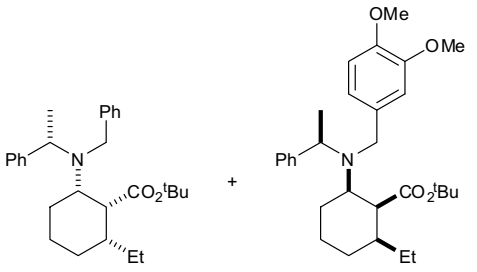
From **34**: $Pd(OH)_2$/C (50 mg, 50% w/w of substrate) was added to a vigorously stirred solution of **34** (100 mg, 0.25 mmol) in degassed MeOH (2.25 mL), and acetone (0.25 mL) at rt under argon. H_2 was bubbled through the solution and the atmosphere of the reaction vessel saturated with H_2 (1 atm). After 24 h, the reaction mixture was filtered through Celite® (eluent EtOAc) and washed with satd aq $NaHCO_3$ (10 mL), dried and concentrated in vacuo to give **37** as a colourless oil (59 mg, 94%, >95% de).

4.25. *tert*-Butyl (1*R*,2*S*,6*R*,α*S*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-6-methyl-cyclohexane-carboxylate 34 and *tert*-butyl (1*S*,2*R*,6*S*,α*R*)-2-[*N*-3′,4′-dimethoxybenzyl-*N*-(α-methylbenzyl)-amino]-6-methyl-cyclohexane-carboxylate 38



Following *General Procedure* 2, BuLi (2.2 M in hexanes, 1.39 mL, 3.02 mmol), (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (323 mg, 1.53 mmol) and (*R*)-*N*-3,4-dimethoxybenzyl-*N*-(α-methylbenzyl)amine (415 mg, 1.53 mmol) in THF (6 mL) and **6** (150 mg, 0.77 mmol) in THF (1.7 mL) gave a 45:45:6:4 mixture of **34**:**38**:**16**:**17**. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 3:1) gave **34** (116 mg, 37%, >98% de) as a wax; $[\alpha]_D^{23} = -92.7$ (*c* 1.0 in $CHCl_3$). Further elution (eluent 30–40 °C petrol/Et_2O, 1:1) gave **38** as a colourless oil (145 mg, 41%, >95% de); $[\alpha]_D^{23} = +80.9$ (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3027, 2959, 1716 (C=O), 1313, 1150; δ_H (400 MHz, $CDCl_3$) 0.83 (3H, d, *J* 6.8, C(6)*Me*), 1.21–1.28 (2H, m, C(4)H_A, C(5)H_A), 1.33 (3H, d, *J* 6.8, C(α)*Me*), 1.35–1.39 (1H, m, C(6)*H*), 1.44 (9H, s, CMe_3), 1.52–1.59 (1H, m, C(5)H_B), 1.60–1.67 (1H, m, C(3)H_A), 1.78–1.84 (1H, m, C(4)H_B), 2.15 (1H, app qd, *J* 12.5, 3.7, C(3)H_B), 2.47 (1H, app t, *J* 4.2, C(1)*H*), 2.66 (1H, app dt, *J* 12.5, 4.2, C(2)*H*), 3.81 (2H, app s, NCH_2), 3.87 (3H, s, O*Me*), 3.93 (3H, s, O*Me*), 4.02 (1H, q, *J* 6.8, C(α)*H*), 6.79 (1H, d, *J* 8.1, C(5′)*H*), 6.92 (1H, app d, *J* 8.1, C(6′)*H*), 7.16 (1H, s, C(2′)*H*), 7.21 (1H, app t, *J* 7.5, *Ph*), 7.31 (2H, app t, *J* 7.5, *Ph*), 7.47 (2H, app d, *J* 7.5, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.2 (C(α)*Me*), 19.4 (C(6)*Me*), 25.3 (*C*(3)), 25.8 (*C*(4)), 28.3 (CMe_3), 28.6 (*C*(5)), 35.1 (*C*(6)), 50.7 (NCH_2), 53.0 (*C*(1)), 55.9, 55.9 (O*Me*), 56.1 (*C*(α)), 59.2 (*C*(2)), 80.4 (*C*Me_3), 110.5 (*C*(5′)), 111.5 (*C*(2′)), 120.1 (*C*(6′)), 126.4 (*p-Ph*), 127.7, 127.8 (*o-Ph*, *m-Ph*), 134.8 (*C*(1′)), 144.6 (*i-Ph*), 147.5 (*C*(4′)), 148.8 (*C*(3′)) 174.1 ($CO_2{}^tBu$); *m*/*z* (ESI^+) 468 ($[M+H]^+$ 100%); HRMS (ESI^+) $C_{29}H_{42}NO_4{}^+$ ($[M+H]^+$) requires 468.3108; found 468.3110.

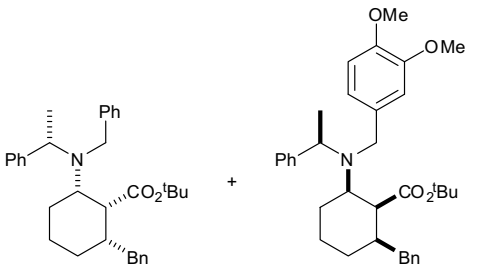
4.26. *tert*-Butyl (1*R*,2*S*,6*R*,α*S*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-6-ethyl-cyclohexane-carboxylate 35 and *tert*-butyl (1*S*,2*R*,6*S*,α*R*)-2-[*N*-3′,4′-dimethoxybenzyl-*N*-(α-methylbenzyl)-amino]-6-ethyl-cyclohexane-carboxylate 39



35 **39**

Following *General Procedure* 2, BuLi (2.2 M in hexanes, 1.70 mL, 3.70 mmol), (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (429 mg, 1.90 mmol) and (*R*)-*N*-3,4-dimethoxybenzyl-*N*-(α-methylbenzyl)amine (514 mg, 1.90 mmol) in THF (8 mL) and **7** (200 mg, 1.19 mmol) in THF (2 mL) gave a 47.5:47.5:3:2 mixture of **35**:**39**:**20**:**21**. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 99:1) gave **35** as a colourless oil (182 mg, 45%, >95% de); $[\alpha]_D^{23} = -64.7$ (*c* 1.0 in $CHCl_3$). Further elution (eluent 30–40 °C petrol/Et_2O, 1:1) gave **39** as a colourless oil (180 mg, 40%, >95% de); $[\alpha]_D^{23} = +65.6$ (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2963, 2933, 1715 (C=O), 1513, 1262, 1142; δ_H (400 MHz, $CDCl_3$) 0.81 (3H, d, *J* 7.2, (C(6)CH_2*Me*), 1.04–1.11 (1H, m, C(6)*H*), 1.13–1.21 (3H, m, C(4)H_A, C(6)CH_2Me), 1.32 (3H, d, *J* 6.7, C(α)*Me*), 1.42–1.47 (1H, m, C(5)H_A), 1.43 (9H, s, C*Me*$_3$), 1.48–1.53 (1H, m, C(5)H_B), 1.60–1.67 (1H, m, C(3)H_A), 1.79–1.86 (1H, m, C(4)H_B), 2.19 (1H, app qd, *J* 12.8, 4.0, C(3)H_B), 2.58 (1H, app t, *J* 4.0, C(1)*H*), 2.64 (1H, app dt, *J* 12.8, 4.0, C(2)*H*), 3.81 (2H, s, NCH_2), 3.87 (3H, s, O*Me*), 3.93 (3H, s, O*Me*), 4.04 (1H, q, *J* 6.7, (C(α)*H*), 6.80 (1H, d, *J* 8.2, C(5′)*H*), 6.93 (1H, d, *J* 8.2, C(6′)*H*), 7.13 (1H, s, C(2′)*H*), 7.21 (1H, app t, *J* 7.4, *Ph*), 7.31 (2H, app t, *J* 7.4, *Ph*), 7.48 (2H, app d, *J* 7.4, *Ph*); δ_C (100 MHz, $CDCl_3$) 11.8 (CH_2*Me*), 14.5 (C(α)*Me*), 25.8, 26.6, 26.7 (*C*(3), *C*(4), *C*(5)), 28.2 (C*Me*$_3$), 29.7 (*C*H$_2$Me), 42.6 (*C*(6)), 50.4 (*C*(1)), 50.7 (N*C*H$_2$), 55.9, 55.9 (O*Me*), 56.2 (*C*(α)), 59.4 (*C*(2)), 80.2 (*C*Me$_3$), 110.6 (*C*(5′)), 111.4 (*C*(2′)), 120.0 (*C*(6′)), 126.4 (*p*-*Ph*), 127.7, 127.8 (*o*-*Ph*, *m*-*Ph*), 134.9 (*C*(1′)), 144.6 (*i*-*Ph*), 147.5 (*C*(4′)), 148.7 (*C*(3′)) 174.0 (*C*O$_2$^{t}Bu); *m*/*z* (ESI$^+$) 482 ([M+H]$^+$ 100%); HRMS (ESI$^+$) $C_{30}H_{44}NO_4^+$ ([M+H]$^+$) requires 482.3265; found 482.3265.

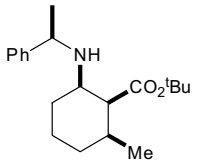
4.27. *tert*-Butyl (1*R*,2*S*,6*S*,α*S*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-6-benzyl-cyclohexane-carboxylate 36 and *tert*-butyl (1*S*,2*R*,6*R*,α*R*)-2-[*N*-3′,4′-dimethoxybenzyl-*N*-(α-methylbenzyl)-amino]-6-benzyl-cyclohexane-carboxylate 40



36 **40**

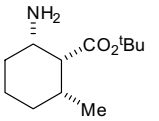
Following *General Procedure* 2, BuLi (2.2 M in hexanes, 1.06 mL, 2.30 mmol), (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (264 mg, 1.18 mmol) and (*R*)-*N*-3,4-dimethoxybenzyl-*N*-(α-methylbenzyl)amine (319 mg, 1.18 mmol) in THF (4 mL) and **8** (160 mg, 0.59 mmol) in THF (2 mL) gave a 47.5:47.5:3:2 mixture of **36**:**40**:**22**:**23**. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 99:1) gave **36** as a colourless oil (117 mg, 41%, >95% de); $[\alpha]_D^{23} = -36.0$ (*c* 1.0 in $CHCl_3$). Further elution with (eluent 30–40 °C petrol/Et_2O, 1:1) gave **40** as a colourless oil (121 mg, 38%, >95% de); $[\alpha]_D^{23} = +26.5$ (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2933, 1715 (C=O), 1513, 1263, 1155; δ_H (400 MHz, $CDCl_3$) 1.10–1.15 (1H, m, C(4)H_A), 1.23–1.27 (1H, m, C(5)H_A), 1.30 (3H, d, *J* 6.7, C(α)*Me*), 1.43–1.48 (1H, m, C(6)*H*), 1.50 (9H, s, C*Me*$_3$), 1.62–1.70 (2H, m, C(3)H_A, C(5)H_B), 1.76–1.83 (1H, m, C(4)H_B), 2.11–2.23 (1H, m, C(3)H_B), 2.34 (1H, dd, *J* 13.5, 8.3, CH_AH$_B$Ph), 2.56 (1H, dd, *J* 13.5, 6.3, CH$_A$$H_B$Ph), 2.61–2.67 (2H, m, C(1)*H*, C(2)*H*), 3.82 (2H, ABq, J_{AB} 14.8, NCH_2), 3.88 (3H, s, O*Me*), 3.92 (3H, s, O*Me*), 4.03 (1H, q, *J* 6.7, C(α)*H*), 6.80 (1H, d, *J* 8.2, C(5′)*H*), 6.93 (1H, d, *J* 8.2, C(6′)*H*), 7.07 (2H, d, *J* 7.2, *Ph*), 7.11 (1H, s, C(2′)*H*), 7.21 (2H, app d, *J* 7.2, *Ph*), 7.27 (4H, app t, *J* 7.2, *Ph*), 7.39 (2H, app d, *J* 7.2, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.2 (C(α)*Me*), 25.7, 25.8, 26.0 (*C*(3), *C*(4), *C*(5)), 28.3 (C*Me*$_3$), 40.3 (*C*H$_2$Ph), 42.7 (*C*(6)), 50.6 (*C*(1)), 50.7 (N*C*H$_2$), 55.9, 55.9 (O*Me*), 56.5 (*C*(α)), 59.8 (*C*(2)), 80.5 (*C*Me$_3$), 110.6 (*C*(5′)), 111.3 (*C*(2′)), 119.9 (*C*(6′)), 125.8, 126.5 (*p*-*Ph*), 127.7, 127.9, 128.1, 129.0 (*o*-*Ph*, *m*-*Ph*), 134.9 (*C*(1′)), 140.6, 144.4 (*i*-*Ph*), 147.5 (*C*(4′)), 148.7 (*C*(3′)) 173.9 (*C*O$_2$^{t}Bu); *m*/*z* (ESI$^+$) 544 ([M+H]$^+$ 100%); HRMS (ESI$^+$) $C_{35}H_{46}NO_4^+$ ([M+H]$^+$) requires 544.3421; found 544.3422.

4.28. *tert*-Butyl (1*S*,2*R*,6*S*,α*R*)-2-[*N*-(α-methylbenzyl)amino]-6-methyl-cyclohexane-carboxylate 41



DDQ (190 mg, 0.85 mmol) was added portionwise to a solution of **38** (190 mg, 0.40 mmol) in DCM (10 mL) and H_2O (2 mL) and the dark red mixture was stirred at rt for 48 h. Satd aq $NaHCO_3$ (15 mL) was added, the layers were separated and the aqueous layer was extracted with DCM (3 × 10 mL). The combined organic layers were washed with brine (50 mL), dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C/Et_2O, 85:15) gave **41** as a colourless oil (84 mg, 66%, >95% de); $[\alpha]_D^{23} = -47.7$ (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3418 (N–H), 2959, 2930, 1723 (C=O), 1451, 1367; δ_H (400 MHz, $CDCl_3$) 0.96 (3H, d, *J* 6.8, C(6)*Me*), 1.12–1.19 (1H, m, C(4)H_A), 1.29 (3H, d, *J* 6.6, C(α)*Me*), 1.39–1.45 (3H, m, C(3)H_A, C(5)H_A, C(6)*H*), 1.52 (9H, s, C*Me*$_3$), 1.55–1.60 (1H, m, C(5)H_B), 1.69–1.83 (2H, m, C(3)H_B, C(4)H_B), 2.41 (1H, app dt, *J* 12.8, 4.9, C(2)*H*), 2.88 (1H, app t, *J* 4.9, C(1)*H*), 4.10 (1H, q, *J* 6.6, (C(α)*H*), 7.23–7.26 (1H, m, *Ph*), 7.31–7.35 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.9 (C(6)*Me*), 24.9 (*C*(4)), 25.5 (C(α)*Me*), 28.4 (C*Me*$_3$), 28.8, 28.9 (*C*(3), *C*(5)), 33.4 (*C*(6)), 50.0 (*C*(1)), 53.8 (*C*(α)), 54.8 (*C*(2)), 80.0 (*C*Me$_3$), 126.4 (*p*-*Ph*), 126.7, 128.4 (*o*-*Ph*, *m*-*Ph*), 146.0 (*i*-*Ph*), 172.7 (*C*O$_2$^{t}Bu); *m*/*z* (ESI$^+$) 318 ([M+H]$^+$ 100%); HRMS (ESI$^+$) $C_{20}H_{32}NO_2^+$ ([M+H]$^+$) requires 318.2428; found 318.2431.

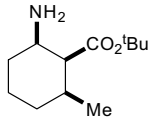
4.29. *tert*-Butyl (1*R*,2*S*,6*R*)-2-amino-6-methyl-cyclohexane-carboxylate 42



Following *General Procedure* 3, $Pd(OH)_2$/C (42 mg, 50% w/w of substrate) and **34** (84 mg, 0.24 mmol) gave (1*R*,2*S*,6*R*)-**42** as a white wax (40 mg, 91%, >95% de); $[\alpha]_D^{23} = -3.7$ (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3374 (N–H), 2931, 1721 (C=O), 1393, 1367, 1150; δ_H (400 MHz, $CDCl_3$) 0.98 (3H, d, *J* 6.9, C(6)*Me*), 1.23–1.29 (1H, m,

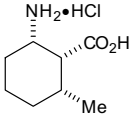
C(5)H_A), 1.31–1.37 (1H, m, C(4)H_A), 1.46 (9H, s, CMe_3), 1.55–1.69 (5H, m, C(3)H_A, C(4)H_B, C(6)H, NH_2), 1.74–1.80 (2H, m, C(3)H_B, C(5)H_B), 2.65 (1H, app t, J 4.8, C(1)H), 2.75–2.82 (1H, m, C(2)H); δ_C (100 MHz, $CDCl_3$) 19.8 (C(6)Me), 24.7 (C(5)), 28.3 (CMe_3), 28.4 (C(4)), 30.5 (C(3)), 34.1 (C(6)), 52.2 (C(2)), 54.2 (C(1)), 80.3 (CMe$_3$), 172.5 ($CO_2{}^tBu$); HRMS (ESI$^+$) $C_{12}H_{24}NO_2^+$ ([M+H]$^+$) requires 214.1802; found 214.1800.

4.30. *tert*-Butyl (1*S*,2*R*,6*S*)-2-amino-6-methyl-cyclohexane-carboxylate 42



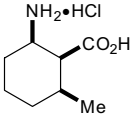
Following *General Procedure* 3, Pd(OH)$_2$/C (30 mg, 50% w/w of substrate) and **41** (62 mg, 0.20 mmol) gave (1*S*,2*R*,6*S*)-**42** as a white wax (37 mg, 88%, >95% de); $[\alpha]_D^{23} = +1.2$ (c 1.0 in $CHCl_3$).

4.31. (1*R*,2*S*,6*R*)-2-Amino-6-methyl-cyclohexane-carboxylic acid hydrochloride 43



Following *General Procedure* 4, TFA (1 mL) and (1*R*,2*S*,6*R*)-**42** (26 mg, 0.12 mmol) in DCM (1 mL), then HCl (2 M in Et$_2$O, 1 mL) and MeOH (1 mL) gave (1*R*,2*S*,6*R*)-**43** as a white powder (22 mg, 92%, >95% de); mp 90–92 °C; $[\alpha]_D^{23} = -2.0$ (c 1.0 in 1 M aq HCl); ν_{max} (KBr) 3114 (NH_3^+), 2962, 2931, 1714 (C=O), 1601, 1203; δ_H (400 MHz, D_2O) 0.90 (3H, d, J 7.0, C(6)Me), 1.16–1.29 (2H, m, C(4)H_A, C(5)H_A), 1.31–1.38 (1H, m, C(5)H_B), 1.63–1.80 (4H, m, C(3)H_2, C(4)H_B, C(6)H), 2.86 (1H, app t, J 4.6, C(1)H), 3.26–3.32 (1H, m, C(2)H); δ_C (100 MHz, D_2O) 19.3 (C(6)Me), 23.5 (C(4)), 25.5 (C(3)), 28.0 (C(5)), 33.8 (C(6)), 47.8 (C(1)), 51.7 (C(2)), 175.0 (CO_2H); HRMS (FI$^+$) $C_8H_{16}NO_2^+$ ([M−Cl]$^+$) requires 158.1176; found 158.1163.

4.32. (1*S*,2*R*,6*S*)-2-Amino-6-methyl-cyclohexane-carboxylic acid hydrochloride 43



Following *General Procedure* 4, TFA (1.5 mL) and (1*S*,2*R*,6*S*)-**42** (30 mg, 0.14 mmol) in DCM (1.5 mL), then HCl (2 M in Et$_2$O, 2 mL) and MeOH (2 mL) gave (1*S*,2*R*,6*S*)-**43** as a white powder (18 mg, 84%, >95% de); $[\alpha]_D^{23} = +1.8$ (c 1.0 in 1 M aq HCl).

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