Tetrahedron 67 (2011) 9975–9992

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Asymmetric synthesis of piperidines and octahydroindolizines using a one-pot ring-closure/*N*-debenzylation procedure

Stephen G. Davies *, Ai M. Fletcher, Deri G. Hughes, James A. Lee, Paul D. Price, Paul M. Roberts, Angela J. Russell, Andrew D. Smith, James E. Thomson, Oliver M.H. Williams

Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford OX1 3TA, UK

ARTICLE INFO

Article history:
Received 1 August 2011
Received in revised form 9 September 2011
Accepted 12 September 2011
Available online 17 September 2011

Dedicated to Professor Gilbert Stork on the occasion of his 90th birthday

Keywords:
Lithium amide
Asymmetric synthesis
Piperidines
Coniine
δ-Coniceine

ABSTRACT

The conjugate addition of an enantiopure lithium amide to a ζ-hydroxy-α,β-unsaturated ester followed by a one-pot ring-closure/N-debenzylation protocol has been used in the asymmetric syntheses of (*S*)-coniine and (*R*)-δ-coniceine (isolated as the corresponding hydrochloride salts), and (*R,R*)-1-(hydroxymethyl)octahydroindolizine (the bicyclic fragment of stellettamides A–C).

1. Introduction

The piperidine skeleton is one of the most common ring systems found in alkaloid natural products. The structures of (+)-coniine **1**, (+)-carpamic acid **2**, (+)-norsedamine **3** and (+)-deoxynojirimycin **4**, for example, are representative of this class of natural products (Fig. 1). Many enantiopure piperidines exhibit potent biological activity,[1] and the broad range of biological activities exhibited by these compounds has meant they have been common targets for synthetic chemists.[2] A key point to address in any synthetic route to enantiopure piperidines is the construction of the azacyclic skeleton in such a manner to enable the desired substitution pattern to be introduced stereoselectively. A large variety of different methods exist to achieve this goal, including the reduction of pyridines,[1c,3] ring-closing metathesis[4] and aza-Diels–Alder reactions,[5] and the synthesis of piperidines has been extensively reviewed.[6]

Previous investigations from our laboratory have demonstrated that the conjugate addition of numerous enantiopure secondary lithium amides (derived from α-methylbenzylamine) to α,β-unsaturated esters represents a general and efficient synthetic protocol for the synthesis of β-amino esters and their derivatives.[7] This methodology has found numerous applications, including the total syntheses of natural products,[8] molecular recognition phenomena[9] and resolution protocols,[10] and has been reviewed.[11] As part of our ongoing research programme in this area we became interested in the application of this methodology for the preparation of enantiopure piperidines and their derivatives and envisaged three approaches towards the piperidine motif: (i) via ring-closing

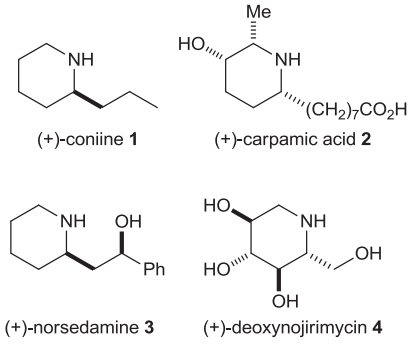
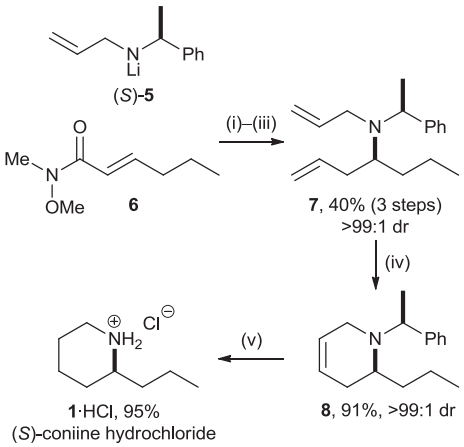


Fig. 1. Piperidine alkaloids **1**–**4**.

* Corresponding author. E-mail address: steve.davies@chem.ox.ac.uk (S.G. Davies).

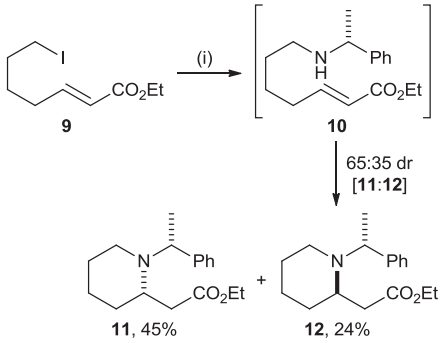
0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.09.038

metathesis of a 4-(*N*-allylamino)alk-1-ene, (ii) via the intramolecular conjugate addition of a lithiated ζ-(*N*-α-methylbenzylamino)-α,β-unsaturated ester and (iii) via cyclisation of a ζ-halo-β-amino ester.[12] We have previously reported the application of the first of these strategies in the synthesis of (*S*)-coniine **1** via the conjugate addition of lithium (*S*)-*N*-allyl-*N*-(α-methylbenzyl)-amide **5** to α,β-unsaturated hydroxamate **6**, followed by ring-closing metathesis of **7** and tandem hydrogenation/hydrogenolysis of the resultant tetrahydropyridine **8** (Scheme 1).[8a] The outcomes of our investigations into the other two strategies are delineated herein; part of this work has been communicated previously.[13]



Scheme 1. Reagents and conditions: (i) THF, −78 °C, 2 h; (ii) DIBAL-H, THF, −78 °C, 30 min; (iii) $NaNH_2$, $[Ph_3PCH_3]^+[Br]^-$, CH_2Cl_2, −40 °C to rt, 4 h; (iv) $RuCl_2(=CHPh)(PCy_3)_2$, CH_2Cl_2, reflux, 12 h; (v) Pd/C, H_2 (5 atm), MeOH, rt, 24 h then HCl.

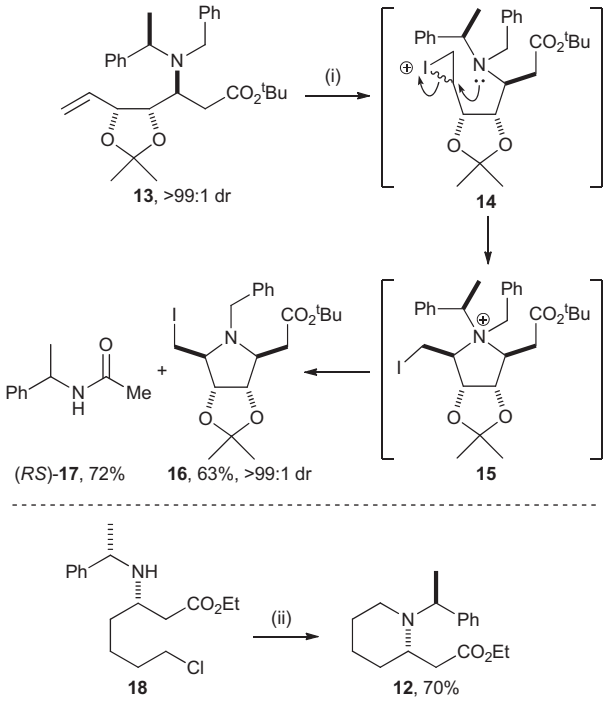
Within the area of intramolecular conjugate additions, diastereoselective 'thermal' additions have previously been reported for the synthesis of piperidines.[14] For example, O'Brien et al. have reported that reaction of (*R*)-α-methylbenzylamine with ζ-iodo-α,β-unsaturated ester **9** gave a 65:35 mixture of piperidines **11** and **12**, which were isolated in 45 and 24% yield, respectively (Scheme 2).[15] We envisaged that kinetically controlled cyclisation of a lithiated ζ-(*N*-α-methylbenzylamino)-α,β-unsaturated ester would provide superior diastereoselectivity relative to the intramolecular 'thermal' additions described above as lithium chelation, present in intermolecular lithium amide conjugate additions,[16] should rigidify the transition state for conjugate addition. We have recently reported a one-pot lithium amide conjugate addition protocol,[7b,17] which involves treating a pre-mixed solution of *N*-benzyl-*N*-(α-methylbenzyl)amine (1.1 equiv) and the requisite α,β-unsaturated ester (1.0 equiv) in THF at −78 °C with BuLi (1.05 equiv).[7b] Similar levels of reaction efficiency were



Scheme 2. Reagents and conditions: (i) (*R*)-α-methylbenzylamine, Et_3N, EtOH, reflux, 16 h.

achieved, relative to the standard stepwise experimental protocol, indicating that alternative processes, such as 1,2-addition or γ-deprotonation of the α,β-unsaturated ester by BuLi do not interfere with the conjugate addition reaction. It was therefore envisaged that this approach could be applicable to the diastereoselective syntheses of azacyclic scaffolds such as 2-substituted pyrrolidines, piperidines and azapanes from the corresponding lithiated ε-, ζ- or η-(*N*-α-methylbenzylamino)-α,β-unsaturated esters.

For our third strategy (cyclisation of a ζ-halo-β-amino ester to give enantiopure piperidine scaffolds) we envisaged that a one-pot procedure may be employed via an intramolecular S_N2-type displacement of the halide by the amino substituent with concomitant loss of the *N*-α-methylbenzyl group. In support of this hypothesis, we have recently reported that iodoamination of **13** upon treatment with I_2 occurs with in situ loss of the *N*-α-methylbenzyl protecting group. The reaction presumably proceeds via reversible iodonium formation and cyclisation to give quaternary ammonium ion **15** that undergoes preferential loss of the *N*-α-methylbenzyl cation, which is then trapped by acetonitrile in a Ritter reaction to give racemic *N*-α-methylbenzylacetamide (*RS*)-**17** in 72% yield, in addition to pyrrolidine **16**, which was isolated in 63% yield and >99:1 dr.[18] Within a similar area, O'Brien et al. have shown that ζ-chloro substituted secondary amino ester **18** undergoes an intramolecular S_N2-type displacement to give piperidine **12** in 70% yield (Scheme 3).[12b]



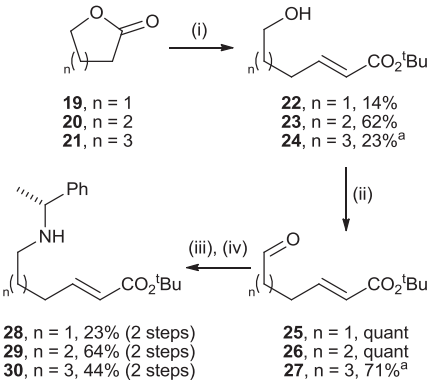
Scheme 3. Reagents and conditions: (i) I_2, $NaHCO_3$, MeCN, rt, 20 h; (ii) K_2CO_3, NaI, EtOH, reflux, 16 h.

2. Results and discussion

2.1. Intramolecular lithium amide conjugate addition

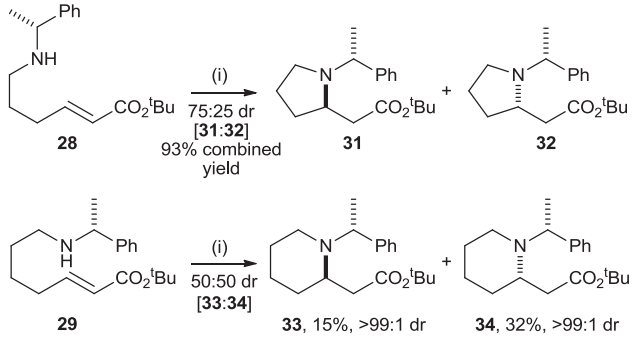
The strategy involving intramolecular conjugate addition of a lithiated ζ-(*N*-α-methylbenzylamino)-α,β-unsaturated ester was investigated first. Substrates **28**–**30** were prepared from the corresponding lactones **19**–**21** via one-pot reduction with DIBAL-H followed by in situ Wadsworth–Emmons olefination. Oxidation

of the resultant ω-hydroxy-α,β-unsaturated esters **22**–**24** with IBX gave aldehydes **25**–**27** in good yield. Subsequent reductive amination of **25**–**27** with (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine and $NaBH(OAc)_3$, followed by chemoselective N-debenzylation of the corresponding tertiary amines using 3.0 equiv of CAN,[19] gave **28**, **29** and **30** in 23, 64 and 44% yield, respectively (Scheme 4).



Scheme 4. Reagents and conditions: (i) BuLi, *tert*-butyl diethylphosphonoacetate, DIBAL-H, THF, −78 °C to rt, 16 h; (ii) IBX, DMSO, rt, 16 h; (iii) $NaBH(OAc)_3$, (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine, THF, 16 h; (iv) CAN, $MeCN/H_2O$ (v/v 5:1), rt, 16 h. [aIsolated in 85:15 dr [(*E*):(*Z*)]; all other compounds were isolated as single diastereoisomers (>99:1 dr)].

With substrates **28**–**30** in hand, the intramolecular lithium amide conjugate addition reactions were attempted. Treating **28** with 1.0 equiv of BuLi resulted in clean cyclisation to give an inseparable 75:25 mixture of pyrrolidines **31** and **32**, respectively, in 93% combined yield.[20] Treatment of **29** with 1.0 equiv of BuLi produced a complex mixture of products containing a 50:50 ratio of piperidines **33** and **34**, respectively, as the major components.[21] Purification of this mixture allowed isolation of **33** in 15% yield and **34** in 32% yield, as single diastereoisomers (>99:1 dr) in each case (Scheme 5). Treating **30** with 1.0 equiv of BuLi gave a complex mixture of unidentifiable products, presumably arising due to intermolecular conjugate addition, consistent with a slower rate of cyclisation for the corresponding seven-membered ring. The apparent lack of diastereoselectivity in this intramolecular case is presumably due to an inability of the lithium amide to adopt the correct geometry for the usual transition state for intermolecular conjugate addition.[16]



Scheme 5. Reagents and conditions: (i) BuLi, THF, −78 °C, 2 h.

2.2. Cyclisation with concomitant N-debenzylation

In our third strategy for the synthesis of enantiopure piperidine scaffolds (cyclisation of a ζ-halo-β-amino ester), it was anticipated that the cyclisation precursors **36** could either be accessed directly from the conjugate addition of an enantiopure lithium amide **39** to ζ-halo-α,β-unsaturated esters **37** (route A) or via the intermediacy of ζ-hydroxy-β-amino esters **38** (route B). ζ-Hydroxy-β-amino esters **38** can be readily produced via the addition of a lithium amide **39** to ζ-hydroxy-α,β-unsaturated ester **23** (Fig. 2).

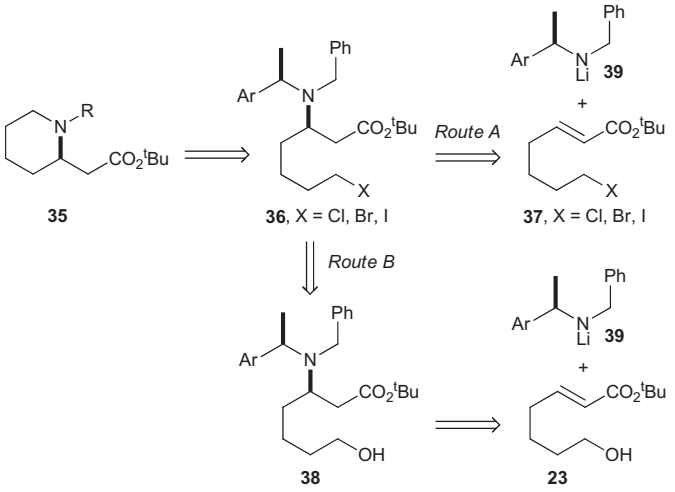
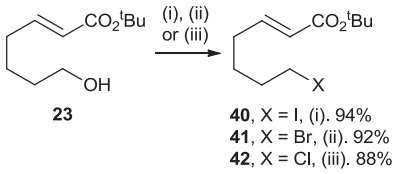


Fig. 2. Retrosynthetic analysis of enantiopure piperidine **35**.

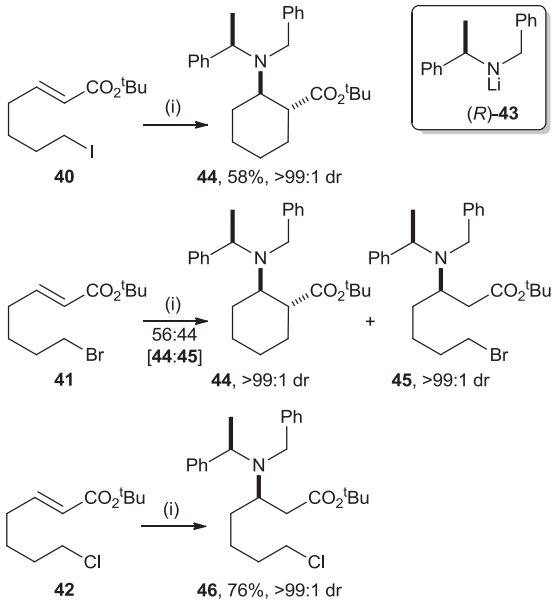
Initial investigations focused upon the conjugate addition of enantiopure lithium amides to ζ-halo substituted α,β-unsaturated esters **40**–**42** (route A, Fig. 2), with subsequent cyclisation of the resultant ζ-halo-β-amino esters via the proposed N-debenzylation strategy. The desired ζ-iodo-, ζ-bromo- and ζ-chloro-α,β-unsaturated esters **40**–**42** were easily synthesised from *tert*-butyl 7-hydroxyhept-2-enoate **23** using standard procedures (Scheme 6).[12a,22]



Scheme 6. Reagents and conditions: (i) PPh_3, imidazole, I_2, PhMe/MeCN (v/v 4:1), 65 °C, 2 h; (ii) PPh_3, CBr_4, CH_2Cl_2, 0 °C to rt, 1 h; (iii) $SOCl_2$, pyridine, 50 °C, 6 h.

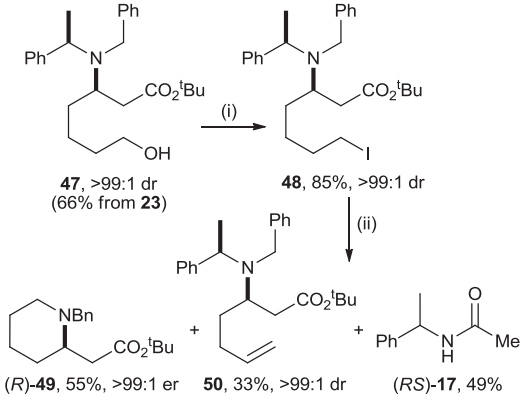
Addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*R*)-**43**[23] to ζ-iodo substituted **40** gave exclusively the known *trans*-hexacin derivative **44**,[24] resulting from intramolecular displacement of the pendant ζ-iodo substituent by the intermediate lithium β-amino enolate, in 58% yield and >99:1 dr. Conjugate addition of (*R*)-**43** to ζ-bromo substituted **41** resulted in formation of an inseparable 56:44 mixture of **44** and ζ-bromo-β-amino ester **45**, respectively, both as single diastereoisomers (>99:1 dr), consistent with the decreased reactivity of the ζ-bromo group towards S_N2-type displacement reactions. Addition of (*R*)-**43** to ζ-chloro substituted **42**, however, gave exclusively the desired ζ-chloro-β-amino ester **46** (>99:1 dr), which was isolated in 76% yield and >99:1 dr after chromatographic purification (Scheme 7).

Attempted cyclisation of **46** with in situ N-debenzylation, which involved heating a solution of **46** in MeCN at 80 °C for 16 h, unfortunately returned only starting material, even in the presence of 1.5 equiv of $AgBF_4$. As the ζ-iodo- and ζ-bromo-substituted α,β-unsaturated esters were proving incompatible with the proposed synthetic route (due to the lability of iodide and bromide groups), and the cyclisation of the ζ-chloro-substrate was not efficacious,



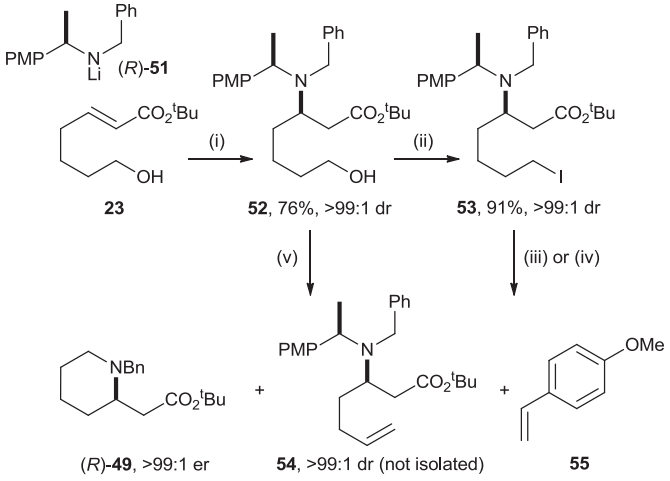
Scheme 7. Reagents and conditions: (i) (*R*)-**43**, THF, −78 °C, 2 h then NH_4Cl (satd aq).

attention turned towards our second strategy involving the synthesis of ζ-halo-β-amino esters from the corresponding ζ-hydroxy-β-amino esters (route B, Fig. 2). Thus, iodination[22b] of **47**[25] [prepared in 66% isolated yield and >99:1 dr upon conjugate addition of (*R*)-**43** to **23**] gave **48** in 85% isolated yield as a single diastereoisomer (>99:1 dr). Heating a solution of **48** in MeCN for 16 h at reflux resulted in formation of a 48:49:3 mixture of starting material **48**, piperidine **49** and ε,ζ-unsaturated β-amino ester **50**, respectively, in addition to racemic *N*-α-methylbenzylacetamide (*RS*)-**17** (resulting from Ritter reaction of the intermediate α-methylbenzyl cation with acetonitrile). However, repetition of this reaction in the presence of 1.5 equiv of $AgBF_4$ resulted in complete consumption of starting material, giving a 63:37 mixture of **49** and **50**, respectively, in addition to (*RS*)-**17**. Purification of this mixture enabled isolation of **49** in 55% yield and >99:1 er,[26] **50** in 33% yield and >99:1 dr, and (*RS*)-**17** in 49% yield (Scheme 8). The formation of **50** in this system is consistent with silver-promoted elimination of HI from within **48**.



Scheme 8. Reagents and conditions: (i) PPh_3, imidazole, I_2, PhMe/MeCN (v/v 4:1), 65 °C, 2 h; (ii) $AgBF_4$, MeCN, 80 °C, 16 h.

Since it was probable that loss of the benzylic cation could be rate-limiting,[27] the corresponding *N*-(*p*-methoxy-α-methylbenzyl) substituted analogue **52**, which was produced in 76% yield and >99:1 dr from the conjugate addition of (*R*)-**51**[28] to **23**, was also investigated. Iodination of **52** upon treatment with 5.0 equiv of PPh_3, I_2 and imidazole[22b] gave ζ-iodo-β-amino ester **53** in 91% yield and >99:1 dr. Subsequent treatment of **53** under the $AgBF_4$ promoted cyclisation conditions gave an 86:14 mixture of **49** and a compound which was tentatively assigned as ε,ζ-unsaturated β-amino ester **54**, although only **49** was isolated in 84% yield after purification. Interestingly, heating a solution of **53** in MeCN at reflux for 16 h (in the absence of $AgBF_4$) caused complete consumption of starting material, to give **49** and *p*-methoxystyrene **55**, which were isolated in 94 and 65% yield, respectively. The one-pot conversion of ζ-hydroxy-β-amino ester **52** into **49** was next attempted by heating a solution of **52** in MeCN in the presence of I_2, PPh_3 and imidazole. Under these conditions cyclisation and in situ N-debenzylation gave piperidine **49** in 75% isolated yield (in three steps and 35% overall yield from δ-valerolactone) and **55** in 33% isolated yield (Scheme 9).



conditions	49:54 ratio	yield of 49	yield of 55
(iii) from **53**	86:14	84%	--
(iv) from **53**	100:0	94%	65%
(v) from **52**	100:0	75%	33%

Scheme 9. Reagents and conditions: (i) THF, −78 °C, 2 h; (ii) PPh_3, imidazole, I_2, PhMe/MeCN (v/v 4:1), 65 °C, 2 h; (iii) $AgBF_4$, MeCN, 80 °C, 16 h; (iv) MeCN, 80 °C, 16 h; (v) PPh_3, imidazole, I_2, MeCN, 80 °C, 16 h. [PMP=*p*-methoxyphenyl].

2.3. Asymmetric syntheses of (*S*)-coniine and (*R*)-δ-coniceine

With methodology for the synthesis of piperidine **49** established, attention was turned towards the elaboration of **49** in the syntheses of the Hemlock alkaloids (*S*)-coniine **1**,[29,30] and (*R*)-δ-coniceine **56**.[31] It was envisaged that (*S*)-coniine **1** could be accessed via a tandem hydrogenation/hydrogenolysis of homoallylamine **57**, which in turn could be synthesised from ester **49** via the intermediacy of aldehyde **58**. Aldehyde **58** was also selected as a suitable precursor for the synthesis of (*R*)-δ-coniceine **56**: it was envisaged that chain extension of **58** would give γ-amino aldehyde **59**, which may then undergo one-pot hydrogenolysis, imine formation and in situ reduction to give (*R*)-δ-coniceine **56** (Fig. 3).

Thus, the *tert*-butyl ester functionality within **49** was fully reduced with DIBAL-H at 0 °C to give alcohol **60** in 99% yield. Subsequent oxidation of **60** under Swern conditions gave β-amino aldehyde **58** in quantitative yield.[32] Wittig reaction of **58** with methyl triphenylphosphonium bromide gave homoallylamine **57** in 52% yield. Tandem hydrogenation/hydrogenolysis of **57** in the presence of Pearlman's catalyst [$Pd(OH)_2$/C] gave, after treatment with HCl, (*S*)-coniine hydrochloride **1**·HCl in 82% yield (Scheme 10).

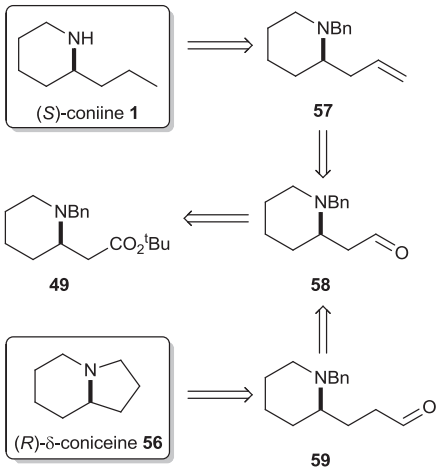
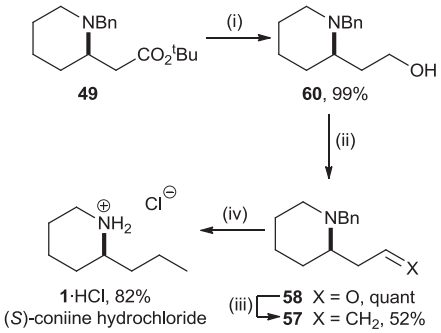


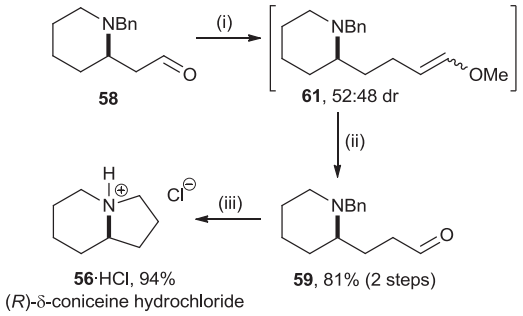
Fig. 3. Retrosynthetic analyses of (*S*)-coniine **1** and (*R*)-δ-coniceine **56**.

The spectroscopic data for (*S*)-coniine hydrochloride **1**·HCl were found to be in excellent agreement with those previously reported in the literature {mp 207–209 °C; lit.[33] mp 214–216 °C; $[\alpha]_D^{23}$ +9.2 (*c* 0.3 in EtOH); lit.[34] $[\alpha]_D^{23}$ +9.4 (*c* 0.3 in EtOH)}.



Scheme 10. Reagents and conditions: (i) DIBAL-H, THF, 0 °C to rt, 6 h; (ii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to rt; (iii) $[Ph_3PMe]^+[Br]^-$, KO^{t}Bu, THF, 0 °C to rt, 16 h; (iv) $Pd(OH)_2/C$ (20% wt), H_2 (1 atm), MeOH, rt, 48 h then HCl.

For the synthesis of (*R*)-δ-coniceine **56**, chain extension of aldehyde **58** via a Wittig reaction with (methoxymethyl)triphenylphosphonium bromide gave enol ether **61** as a 52:48 mixture of geometric isomers. Hydrolysis of this mixture gave γ-amino aldehyde **59** in 81% yield (from **58**), which upon treatment with Pearlman's catalyst under 1 atm of H_2 gave (*R*)-δ-coniceine **56**, which was isolated as the corresponding hydrochloride salt in 94% yield (Scheme 11).



Scheme 11. Reagents and conditions: (i) $[Ph_3PCH_2OMe]^+[Br]^-$, KO^{t}Bu, THF, 0 °C to rt, 16 h; (ii) CH_2Cl_2/HCO_2H (v/v 4:1), rt, 16 h; (iii) $Pd(OH)_2/C$ (20% wt), H_2 (1 atm), MeOH, rt, 48 h then HCl.

2.4. Synthesis of functionalised octahydroindolizines

Investigations into the alkylation of piperidine **49** to allow access to more functionalised natural products, based on an indolizine scaffold, were next undertaken. 1-(Hydroxymethyl)octahydroindolizine **62** was identified as a potential target as it possesses the correct configuration for the heterocyclic core fragment of the octahydroindolizine alkaloids stellettamides A–C **63**–**65** (Fig. 4).[2d,35] Stellettamides A–C **63**–**65** were all isolated from marine sponges of the genus *Stelleta* and share the common (1*S*,4*S*,8a*R*)-1-amidomethyl-*N*(4)-methylindolizidine architectural motif.[2d,35c] Stellettamide A **63** was the first of these alkaloids isolated (by Fusetani et al. in 1990) and displays antifungal and cytotoxic activity.[35a] Several total syntheses of these compounds have recently been reported, allowing the absolute configurations within **63**–**65** to be established unambiguously.

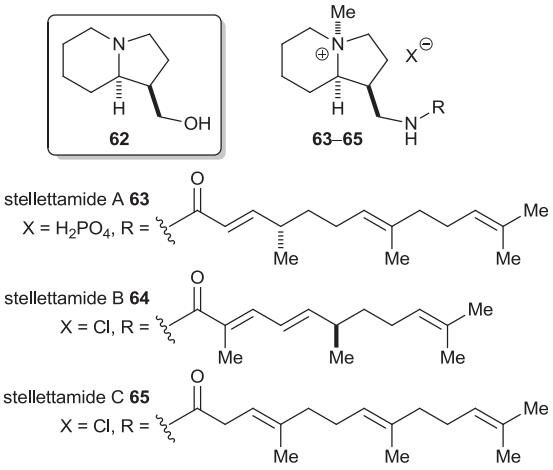
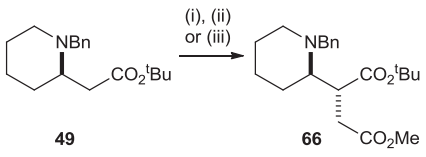


Fig. 4. The structures of stelletamides A–C **63**–**65**, incorporating a 1-(amidomethyl)-octahydroindolizine heterocyclic core.

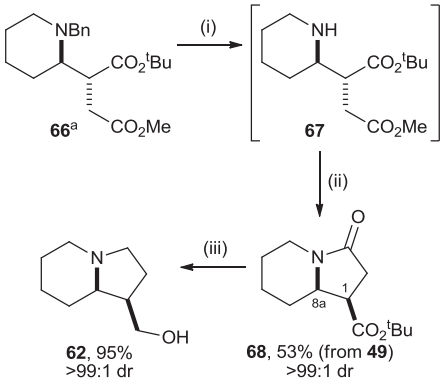
Initial investigations towards the alkylation of ester **49** employed 2.0 equiv of LiTMP and 3.0 equiv of methyl bromoacetate, which gave **66** in 90:10 dr (70% conversion). Purification of the crude reaction mixture gave an inseparable 77:23 mixture of **66** (98:2 dr) and starting material **49**, respectively. The stereochemical outcome of the alkylation reaction was initially assigned by analogy to previous alkylations of β-amino enolates.[15,36] Unfortunately, attempts to improve the reaction conversion by employing alternative bases was not successful: attempted alkylation of **49** upon treatment with 1.5 equiv of LiHMDS and 2.0 equiv of methyl bromoacetate resulted in 69% conversion to **66** (86:14 dr), whereas treatment of **49** with 2.0 equiv of LDA and 3.0 equiv of methyl bromoacetate led to improved conversion, but with a decrease in diastereoselectivity giving **66** in 80:20 dr (Scheme 12).



	Base	Conv (%)	dr
(i)	LiTMP	70	90:10
(ii)	LiHMDS	69	86:14
(iii)	LDA	85	80:20

Scheme 12. Reagents and conditions: (i) BuLi, HTMP, $BrCH_2CO_2Me$, THF, −78 °C to rt, 16 h; (ii) LiHMDS, $BrCH_2CO_2Me$, THF, −78 °C to rt, 4 h; (iii) BuLi, ^{i}Pr$_2$NH, $BrCH_2CO_2Me$, THF, −78 °C to rt, 16 h.

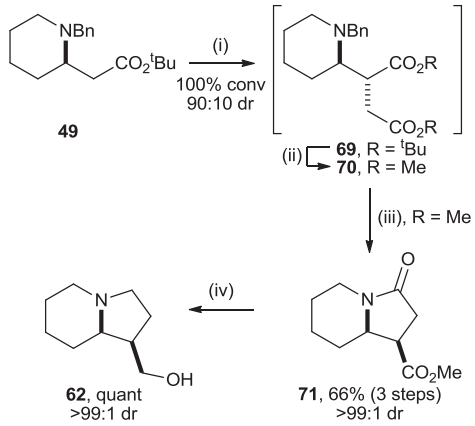
Treating the 77:23 mixture of **66** (98:2 dr) and **49**, respectively, under hydrogenolysis conditions led to successful debenzylation of **66**, and also partial cyclisation of secondary amino ester **67** to give hexahydroindolizin-3-one **68**.[37] Complete cyclisation of **67** to **68** was achieved by heating the crude product mixture in $CHCl_3$ for 16 h.[38] Hexahydroindolizin-3-one **68** was duly obtained as a single diastereoisomer (>99:1 dr) in 53% yield (from **49**) after chromatographic purification (Scheme 13). The relative configuration within **68** was then confirmed by ^{1}H NMR NOE analysis, which showed strong reciprocal enhancements between the C(1)*H* and C(8a)*H* protons. With **68** in hand, it was predicted that reduction with $LiAlH_4$ would generate the corresponding 1-(hydroxymethyl)-octahydroindolizine **62**. Thus, tandem reduction of the amide and ester groups within **68** with $LiAlH_4$ gave (*R*,*R*)-1-(hydroxymethyl)-octahydroindolizine **62** in 95% yield and >99:1 dr (Scheme 13).



Scheme 13. Reagents and conditions: (i) $Pd(OH)_2/C$, H_2 (1 atm), MeOH, rt, 48 h; (ii) $CHCl_3$, reflux, 16 h; (iii) $LiAlH_4$, THF, reflux, 16 h. [[a]77:23 mixture of **66** (98:2 dr) and **49**].

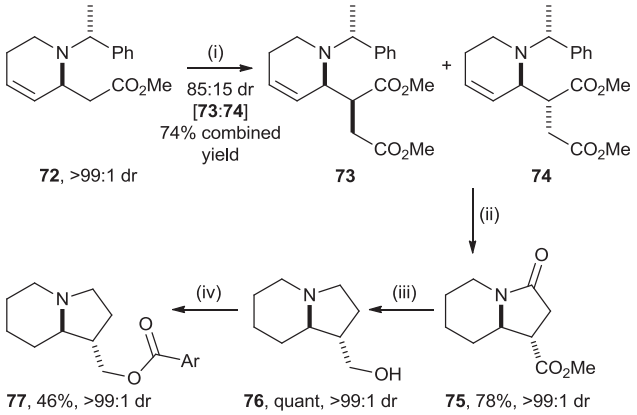
Both diastereoisomers of 1-(hydroxymethyl)octahydroindolizine have previously been reported,[39] although some discrepancies exist between the various spectroscopic data for these compounds in the literature. We therefore sought to unambiguously clarify these apparent discrepancies by producing several derivatives of **62** (and the corresponding epimer) for attempted recrystallisation and analysis by X-ray diffraction. Upon scale-up an optimized procedure for the preparation of **62** was developed: alkylation of **49** with *tert*-butyl bromoacetate gave **69** in quantitative conversion and 90:10 dr. Subsequent transesterification of **69** upon treatment with HCl in MeOH gave **70**, which upon deprotection of the *N*-benzyl group gave hexahydroindolizin-3-one **71** in >99:1 dr and 66% overall yield (three steps). Reduction of **71** with $LiAlH_4$ then gave **62** in quantitative yield and >99:1 dr; this synthetic sequence was readily achieved on a >1 g scale (Scheme 14).

Unfortunately all attempts to crystallise derivatives of **62** for single crystal X-ray diffraction analysis were unsuccessful. However, we were able to obtain a sample of the epimeric 1-(hydroxymethyl)octahydroindolizine **76** via an alternative procedure: it was observed that alkylation of **72** (prepared previously as part of our synthetic endeavours towards the *Sedum* alkaloids[8h]) with methyl bromoacetate proceeded with complementary diastereoselectivity to the alkylations of **49**, giving an 85:15 mixture of *syn*-**73** and *anti*-**74**, respectively, which was isolated in 74% combined yield. Treating this mixture under standard hydrogenolysis conditions gave, after chromatographic purification, *anti*-**75** as a single diastereoisomer (>99:1 dr) in 78% isolated yield;[40] the spectroscopic data for **75** were clearly distinct from those of the epimeric hexahydroindolizin-3-one **71**. Treatment of **75** with



Scheme 14. Reagents and conditions: (i) BuLi, HTMP, $BrCH_2CO_2{}^tBu$, THF, −78 °C to rt, 16 h; (ii) 1.35 M HCl in MeOH, 60 °C, 16 h; (iii) $Pd(OH)_2/C$, H_2 (1 atm), MeOH, rt, 24 h; (iv) $LiAlH_4$, THF, reflux, 48 h.

$LiAlH_4$ gave **76** in quantitative yield and >99:1 dr, and conversion to the *p*-nitrobenzoate derivative **77** produced crystals suitable for X-ray diffraction analysis (Scheme 15). These crystallographic data (Fig. 5) unambiguously established the relative configuration within **77** (and also those within **62**, **66**–**71**, and **73**–**76**), with the absolute configurations assigned relative to the known diastereofacial selectivity observed upon conjugate addition of an enantiopure lithium amide.[11]



Scheme 15. Reagents and conditions: (i) NaHMDS, THF, −78 °C, 30 min then $BrCH_2CO_2Me$, −78 °C to rt, 16 h; (ii) $Pd(OH)_2/C$ (50% wt), H_2 (1 atm), MeOH, rt, 16 h then $NaHCO_3$ (satd, aq); (iii) $LiAlH_4$, 60 °C, THF, 3 days; (iv) *p*-$NO_2C_6H_4COCl$, CH_2Cl_2, Et_3N, rt, 20 h. [Ar=*p*-$NO_2C_6H_4$].

Whilst our data are unambiguous, agree with those of Martin[39e] and Pandey,[39c] and are broadly consistent with those of Nagao,[39a] it appears that Hoffmann and Pete,[39d,g] have misassigned the configuration within their 1-(hydroxymethyl)octahydroindolizidine product since their data are not consistent with any stereoisomer (Table 1). Although the discrepancy in the values of the specific rotations for **76** remains unexplained, the stereochemical assignments for both our samples of (−)-(*R*,*R*)-**62** and (+)-(1*S*,8a*R*)-**76** are secure.

3. Conclusion

In conclusion, a one-pot ring-closure with concomitant N-debenzylation protocol has been developed for the synthesis of an enantiopure piperidine scaffold. The conjugate addition of an enantiopure lithium amide to a ζ-hydroxy-α,β-unsaturated ester,

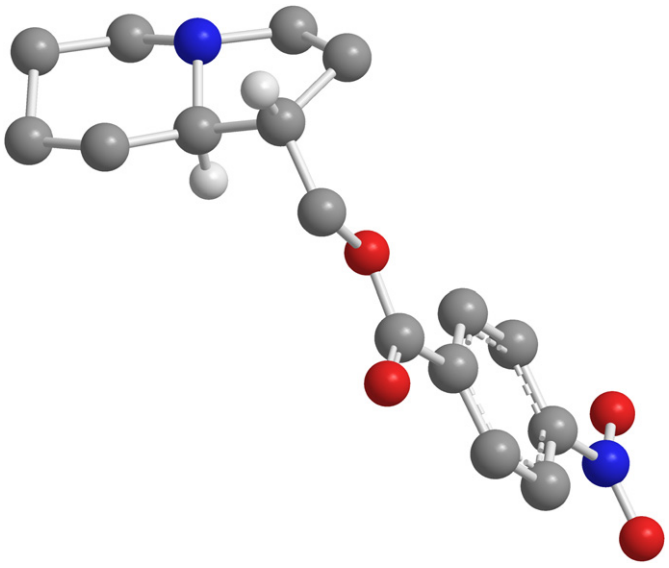


Fig. 5. Chem3D representation of the X-ray crystal structure of **77** (selected H atoms are omitted for clarity).

followed by heating a solution of the corresponding ζ-hydroxy-β-amino ester in MeCN in the presence of I_2, PPh_3 and imidazole, promoted cyclisation and in situ N-debenzylation to give *tert*-butyl (*R*)-(*N*-benzylpiperidin-2′-yl)acetate in 75% isolated yield (in three steps and 35% overall yield from commercially available δ-valerolactone). Subsequently, the total asymmetric syntheses of (*S*)-coniine and (*R*)-δ-coniceine (isolated as the corresponding hydrochloride salts), and (*R*,*R*)-1-(hydroxymethyl)octahydroindolizine (the bicyclic core of stellettamides A–C) were achieved via elaboration of this enantiopure piperidine template. Furthermore, a sample of (1*S*,8a*R*)-1-(hydroxymethyl)octahydroindolizine was also produced by a complementary procedure; X-ray diffraction analysis of the corresponding *p*-nitrobenzoate derivative unambiguously clarified the existing literature discrepancies between the spectroscopic data for both these 1-(hydroxymethyl)octahydroindolizines.

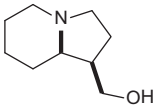
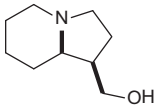
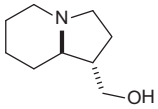
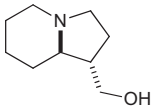
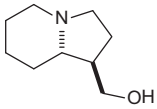
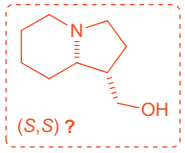
4. Experimental

4.1. General experimental

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. BuLi was purchased from Sigma–Aldrich (as a solution in hexanes) and titrated against diphenylacetic acid before use. Solvents were dried according to the procedure outlined by Grubbs et al.[39] Water was purified by an Elix® UV-10 system. All other 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.

Elemental analyses were recorded by the microanalysis service of the Inorganic Chemistry Laboratory, University of Oxford, UK. 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 a Bruker Tensor 27 FT-IR spectrometer as either a thin film on NaCl plates (film) or a KBr

Table 1
Spectroscopic data for **62** and **76**

Authors	Pandey[a]	Davies	Davies		Martin	Nagao	Hoffmann and Pete[b]
Structure							
Configuration	(*RS*,*RS*)-**62**	(*R*,*R*)-**62**	(1*S*,8a*R*)-**76**		(1*RS*,8a*SR*)-**76**	(1*R*,8a*S*)-**76**	
Specific Rotation	Racemic	$[\alpha]_D^{23}$ −35.8 (*c* 0.5 in EtOH)	$[\alpha]_D^{23}$ +27.4 (*c* 1.0 in EtOH)		Racemic	$[\alpha]_D^{22}$ −53.4 (*c* 1.2 in EtOH)	$[\alpha]_D^{21}$ −82.1 (*c* 1.0 in EtOH)
NMR solvent	$CDCl_3$	$CDCl_3$	$CDCl_3$	CD_3CN	CD_3CN	$CDCl_3$	$CDCl_3$
^{1}H NMR data	0.95–2.55 (12H)	1.13–1.37 (2H)	1.10–1.32 (2H)	1.14–1.26 (2H)	1.13–1.20 (2H)	1.05–2.36 (12H)	0.94–2.29 (8H)
		1.40–1.69 (3H)	1.40–1.49 (1H)	1.35–1.65 (4H)	1.33–1.61 (4H)		
		1.74–1.87 (4H)	1.50–1.65 (3H)	1.71–1.89 (4H)	1.71–1.87 (4H)		
		1.90–2.13 (3H)	1.72–1.82 (1H)	1.91–1.98 (1H)	1.90–1.96 (1H)		2.36–2.69 (4H)
	2.95–3.30 (3H)	3.05–3.40 (2H)	1.84–2.08 (4H)	2.05 (1H)	2.05 (1H)	2.80–3.38 (2H+O*H*)	3.01–3.16 (1H)
	3.33–3.65 (2H)	3.46 (1H)	2.15–2.20 (1H)	2.45 (O*H*)	2.60 (1H)		3.21–3.42 (1H)
		3.86 (1H)	2.26 (O*H*)	2.86–2.92 (1H)	2.88–2.91 (1H)	3.63 (2H)	3.58–3.68 (2H)
		3.95 (O*H*)	2.99–3.10 (2H)	2.94–3.02 (1H)	2.97 (1H)		4.51 (1H)
			3.56–3.65 (2H)	3.41–3.51 (2H)	3.41–3.49 (2H)		
^{13}C NMR data	24.2[a]	24.1	24.3	24.7	25.2	24.3	24.3
	25.6	25.3	25.2	25.7	26.1	25.2	25.2
	26.9	25.4	25.3	25.8	26.3	25.4	25.4
	29.5	26.7	30.5	30.9	31.2	30.4	30.4
	41.2	41.0	46.1	46.7	47.2	46.1	46.1
	53.3	53.6	53.4	53.3	53.8	53.1	53.1
	53.8	53.9	53.9	53.6	54.1	53.4	53.4
	64.2[a]	64.6	64.9	64.3	64.7	64.6	64.6
	64.7	66.2	67.3	67.6	68.2	67.4	67.4
Ref.	39c				39e	39a	39d

[a] The authors have kindly confirmed that there is a peak missing at 24.15 ppm in their reported ^{13}C NMR data and that the value of '54.17 ppm' was reported in error. The corrected values, as supplied by Pandey et al., are shown here.

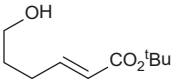
[b] The authors are confident (personal communication, N. Hoffmann) that the (1*S*)-configuration for their compound is correct, but the relative configuration is probably erroneous. However, their data do not support any stereochemical assignment.

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. Spectra were recorded at rt. The field was locked by external referencing to the relevant deuteron resonance. 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: lithium amide conjugate addition

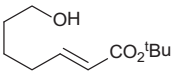
BuLi was added dropwise to a stirred solution of the requisite amine in the THF at −78 °C. After 30 min, a solution of the requisite α,β-unsaturated ester in THF was added via cannula. The reaction mixture was stirred at −78 °C for 2 h and then satd aq NH_4Cl was added. The resultant mixture was concentrated in vacuo and extracted with three portions of Et_2O. The combined organic extracts were dried and concentrated in vacuo. The residue was dissolved in CH_2Cl_2, the resultant solution was washed with 10% aq citric acid, satd aq $NaHCO_3$ and brine, then dried and concentrated in vacuo.

4.2.1. *tert*-Butyl (*E*)-6-hydroxyhex-2-enoate **22**.



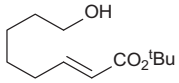
BuLi (45.5 mL, 113.3 mmol) was added dropwise to a solution of *tert*-butyl diethylphosphonoacetate (28.3 g, 112 mmol) in THF (50 mL) at −78 °C. The resultant solution was stirred for 30 min at −78 °C then a solution of **19** (8.78 g, 102 mmol) in THF (25 mL) at −78 °C was added via cannula followed by the dropwise addition of DIBAL-H (1.0 M in THF, 100 mL, 100 mmol). The reaction mixture was allowed to warm to rt over 16 h, then satd aq sodium potassium tartrate (5 mL) was added. The reaction mixture was partitioned between EtOAc (30 mL) and 0.5 M aq HCl (30 mL). The organic layer was washed with satd aq K_2CO_3 (30 mL) and brine (30 mL), then dried and concentrated in vacuo to give **22** (98:2 dr [(*E*)/(*Z*)]). Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 2:1) gave **22** as a colourless oil (2.67 g, 14%, >99:1 dr [(*E*)/(*Z*)]);[25] ν_{max} (film) 3428 (O–H), 1715 (C=O), 1653 (C=C); δ_H (400 MHz, $CDCl_3$) 1.48 (9H, s, CMe_3), 1.69–1.76 (2H, m, C(5)H_2), 2.24–2.31 (2H, app dq, *J* 6.9, 1.3, C(4)H_2), 3.67 (2H, dt, *J* 6.6, 1.3, C(6)H_2), 5.74 (1H, d, *J* 15.2, C(2)*H*), 6.87 (1H, dt, *J* 15.2, 6.9, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 28.1 (CMe_3), 28.3 (*C*(5)), 31.0 (*C*(4)), 62.0 (*C*(6)), 82.5 (*C*Me$_3$), 123.5 (*C*(2)), 147.0 (*C*(3)), 173.1 (*C*(1)); *m*/*z* (CI^+) 187 ($[M+H]^+$, 100%); HRMS (CI^+) $C_{10}H_{19}O_3^+$ ($[M+H]^+$) requires 187.1329; found 187.1335.

4.2.2. *tert*-Butyl (*E*)-7-hydroxyhept-2-enoate **23**.



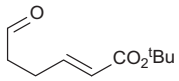
BuLi (13.6 mL, 34.0 mmol) was added dropwise to a solution of *tert*-butyl diethylphosphonoacetate (8.49 g, 33.7 mmol) in THF (20 mL) at −78 °C. The resultant solution was stirred for 30 min at −78 °C then a solution of **20** (3.06 g, 30.6 mmol) in THF (10 mL) at −78 °C was added via cannula followed by the dropwise addition of DIBAL-H (1.0 M in THF, 30.0 mL, 30.0 mmol). The reaction mixture was allowed to warm to rt over 16 h, then satd aq sodium potassium tartrate (5 mL) was added. The reaction mixture was then partitioned between EtOAc (30 mL) and 0.5 M aq HCl (30 mL). The organic layer was washed with satd aq K_2CO_3 (30 mL) and brine (30 mL), then dried and concentrated in vacuo to give **23** (96:4 dr [(*E*)/(*Z*)]). Purification via flash column chromatography (eluent 30–40 °C petrol:Et_2O, 2:1) gave **23** as a colourless oil (3.78 g, 62%, >99:1 dr [(*E*)/(*Z*)]);[41] δ_H (400 MHz, $CDCl_3$) 1.48 (9H, s, CMe_3), 1.55–1.65 (4H, m, C(5)H_2, C(6)H_2), 2.18–2.25 (2H, app dq, *J* 6.9, 1.4, C(4)H_2), 3.66 (2H, t, *J* 6.6, C(7)H_2), 5.75 (1H, d, *J* 15.6, C(2)*H*), 6.85 (1H, dt, *J* 15.6, 6.9, C(3)*H*).

4.2.3. *tert*-Butyl (*E*)-8-hydroxyoct-2-enoate **24**.



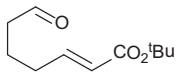
BuLi (3.89 mL, 9.72 mmol) was added dropwise to a solution of *tert*-butyl diethylphosphonoacetate (2.43 g, 8.76 mmol) in THF (15 mL) at −78 °C. The resultant solution was stirred for 30 min at −78 °C then a solution of **21** (1.00 g, 8.76 mmol) in THF (5 mL) at −78 °C was added via cannula followed by the dropwise addition of DIBAL-H (1.0 M in THF, 8.58 mL, 8.58 mmol). The reaction mixture was allowed to warm to rt over 16 h, then satd aq sodium potassium tartrate (5 mL) was added. The reaction mixture was then partitioned between EtOAc (30 mL) and 0.5 M aq HCl (30 mL). The organic layer was washed with satd aq K_2CO_3 (30 mL) and brine (30 mL), then dried and concentrated in vacuo to give **24** (92:8 dr [(*E*)/(*Z*)]). Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 1:0; increased to 30–40 °C petrol/Et_2O, 2:1) gave **24** as a colourless oil (500 mg, 23%, 85:15 dr [(*E*)/(*Z*)]); ν_{max} (film) 3413 (O–H), 1715 (C=O), 1652 (C=C); δ_H (400 MHz, $CDCl_3$) 1.36–1.53 (4H, m, C(5)H_2, C(6)H_2), 1.48 (9H, s, CMe_3), 1.54–1.62 (2H, m, C(7)H_2), 2.15–2.22 (2H, app dq, *J* 6.9, 1.3, C(4)H_2), 3.65 (2H, t, *J* 6.6, C(8)H_2), 5.74 (1H, d, *J* 15.5, C(2)*H*), 6.85 (1H, dt, *J* 15.5, 6.9, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 25.3, 27.9 (*C*(5), *C*(6)), 28.1 (CMe_3), 32.0 (*C*(4)), 32.5 (*C*(7)), 62.8 (*C*(8)), 80.1 (*C*Me$_3$), 123.1 (*C*(2)), 147.8 (*C*(3)), 166.2 (*C*(1)); *m*/*z* (CI^+) 232 ($[M+NH_4]^+$, 100%); HRMS (CI^+) $C_{12}H_{26}NO_3^+$ ($[M+NH_4]^+$) requires 232.1907; found 232.1920.

4.2.4. *tert*-Butyl (*E*)-6-oxohex-2-enoate **25**.



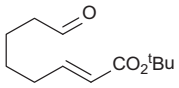
IBX (2.26 g, 8.06 mmol) was added to a solution of **22** (500 mg, 0.269 mmol, >99:1 dr [(*E*)/(*Z*)]) in DMSO (10 mL) and the resultant mixture was stirred at rt for 16 h. Et_2O (50 mL) was then added and the organic layer was washed with H_2O (4×40 mL). The organic layer was then dried and concentrated in vacuo to give **25** as a colourless oil (494 mg, quant, >99:1 dr [(*E*)/(*Z*)]);[25] δ_H (400 MHz, $CDCl_3$) 1.48 (9H, s, CMe_3), 2.48–2.54 (2H, app q, *J* 6.9, C(4)H_2), 2.63 (2H, dt, *J* 6.9, 0.9, C(5)H_2), 5.78 (1H, dt, *J* 15.7, 1.1, C(2)*H*), 6.84 (1H, dt, *J* 15.7, 6.9, C(3)*H*), 9.80 (1H, app s, C(6)*H*).

4.2.5. *tert*-Butyl (*E*)-7-oxohept-2-enoate **26**.



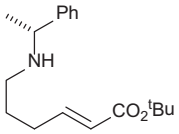
IBX (420 mg, 1.50 mmol) was added to a solution of **23** (100 mg, 0.50 mmol, >99:1 dr [(*E*)/(*Z*)]) in DMSO (2 mL) and the resultant mixture was stirred at rt for 16 h. Et_2O (15 mL) was then added and the organic layer was washed with H_2O (4×25 mL). The organic layer was then dried and concentrated in vacuo to give **26** as a colourless oil (99 mg, quant, >99:1 dr [(*E*)/(*Z*)]);[42] δ_H (400 MHz, $CDCl_3$) 1.48 (9H, s, CMe_3), 1.77–1.85 (2H, app quintet, *J* 7.0, C(5)H_2), 2.20–2.26 (2H, app dq, *J* 7.0, 1.5, C(4)H_2), 2.49 (2H, dt, *J* 7.0, 1.3, C(6)H_2), 5.77 (1H, dt, *J* 15.6, 1.5, C(2)*H*), 6.82 (1H, dt, *J* 15.6, 7.0, C(3)*H*), 9.79 (1H, t, *J* 1.3, C(7)*H*).

*4.2.6. tert-Butyl (E)-8-oxooct-2-enoate **27**.*



IBX (687 mg, 2.45 mmol) was added to a solution of **24** (175 mg, 0.818 mmol, 85:15 dr [(*E*)/(*Z*)]) in DMSO (5.0 mL) and the resultant mixture was stirred at rt for 16 h. Et_2O (30 mL) was then added and the organic layer was washed with H_2O (4×20 mL). The organic layer was then dried and concentrated in vacuo to give **27** as a colourless oil (123 mg, 71%, 85:15 dr [(*E*)/(*Z*)]); ν_{max} (film) 1714 (C=O), 1653 (C=C); δ_H (400 MHz, $CDCl_3$) 1.47–1.53 (2H, m, C(5)H_2), 1.48 (9H, s, CMe_3), 1.61–1.70 (2H, m, C(6)H_2), 2.16–2.23 (2H, m, C(4)H_2), 2.45 (2H, dt, *J* 7.2, 1.3, C(7)H_2), 5.74 (1H, td, *J* 15.6, 1.5, C(2)*H*), 6.82 (1H, td, *J* 15.6, 6.9, C(3)*H*), 9.76 (1H, app s, C(8)*H*); δ_C (100 MHz, $CDCl_3$) 21.5 (*C*(6)), 27.5 (*C*(5)), 28.1 (CMe_3), 31.7 (*C*(4)), 48.6 (*C*(7)), 80.1 (*C*Me_3), 123.4 (*C*(2)), 147.0 (*C*(3)), 166.0 (*C*(1)), 202.2 (*C*(8)); *m*/*z* (CI^+) 230 ($[M+NH_4]^+$, 100%); HRMS (CI^+) $C_{12}H_{24}NO_3^+$ ($[M+NH_4]^+$) requires 230.1751; found 230.1748.

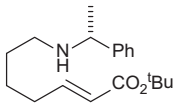
*4.2.7. tert-Butyl (E,R)-6-[N-(α-methylbenzyl)amino]hex-2-enoate **28**.*



Step 1: $NaBH(OAc)_3$ (854 mg, 4.03 mmol) was added to a solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (851 mg, 4.03 mmol) and **25** (495 mg, 2.69 mmol, >99:1 dr [(*E*)/(*Z*)]) in THF (10 mL) and the resultant solution was stirred at rt for 16 h. 1.0 M aq NaOH (10 mL) was then added and the aqueous layer was extracted with EtOAc (40 mL). The combined organic layers were then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 15:1) gave *tert*-butyl (*E*,*R*)-6-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-2-enoate as a colourless oil (282 mg, 28%, >99:1 dr [(*E*)/(*Z*)]); $C_{25}H_{33}NO_2$ requires C, 79.1; H, 8.8; N, 3.7%; found C, 79.1; H, 8.8; N, 3.5%; $[\alpha]_D^{23}$ +29.9 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1713 (C=O); δ_H (400 MHz, $CDCl_3$) 1.40 (3H, d, *J* 6.8, C(α)*Me*), 1.50 (9H, s, CMe_3), 1.54–1.63 (2H, m, C(5)H_2), 2.02–2.19 (2H, app q, *J* 7.2, C(4)H_2), 2.34–2.42 (1H, m, C(6)H_A), 2.53–2.60 (1H, m, C(6)H_B), 3.53 (1H, d, *J* 14.0, NC$H_A$$H_B$Ph), 3.60 (1H, d, *J* 14.0, NCH$_A$$H_B$Ph), 3.93 (1H, q, *J* 6.8, C(α)*H*), 5.65 (1H, dd, *J* 15.6, 1.2, C(2)*H*), 6.79 (1H, dt, *J* 15.6, 7.2, C(3)*H*), 7.22–7.44 (10H, m, 2×*Ph*); δ_C (100 MHz, $CDCl_3$) 14.9 (C(α)*Me*), 26.0 (*C*(5)), 28.2 (CMe_3), 29.7 (*C*(4)), 48.7 (*C*(6)), 54.5 (NCH_2Ph), 57.8 (*C*(α)), 79.9 (*C*Me_3), 122.9 (*C*(2)), 126.7, 127.9, 128.0, 128.2, 128.6 (2×*o*,*m*,*p*-*Ph*), 140.8, 143.6 (2×*i*-*Ph*), 147.9 (*C*(3)), 166.1 (*C*(1)); *m*/*z* (ESI^+) 380 ($[M+H]^+$, 100%).

Step 2: CAN (568 mg, 1.04 mmol) was added to a solution of *tert*-butyl (*E*,*R*)-6-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-2-enoate (131 mg, 0.35 mmol, >99:1 dr [(*E*)/(*Z*)]) in MeCN/H_2O (v/v 5:1, 6 mL) and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then diluted with Et_2O (20 mL), satd aq $NaHCO_3$ was added (20 mL), and stirring was continued for a further 30 min. The aqueous layer was extracted with Et_2O (2×20 mL) and the combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (gradient elution, 0→30% Et_2O in 30–40 °C petrol) gave **28** as a yellow oil (83 mg, 83%, >99:1 dr [(*E*)/(*Z*)]); $[\alpha]_D^{23}$ +39.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3375 (N–H), 1714 (C=O), 1653 (C=C); δ_H (400 MHz, $CDCl_3$) 1.37 (3H, d, *J* 6.6, C(α)*Me*), 1.50 (9H, s, CMe_3), 1.59–1.66 (2H, m, C(5)H_2), 2.16–2.26 (2H, app q, *J* 6.9, C(4)H_2), 2.43–2.49 (1H, m, C(6)H_A), 2.43–2.49 (1H, m, C(6)H_B), 3.77 (1H, q, *J* 6.6, C(α)*H*), 5.74 (1H, dt, *J* 15.8, 1.6, C(2)*H*), 6.84 (1H, dt, *J* 15.8, 6.9, C(3)*H*), 7.24–7.37 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 24.4 (C(α)*Me*), 28.1 (CMe_3), 28.7 (*C*(5)), 29.8 (*C*(4)), 47.1 (*C*(6)), 58.3 (*C*(α)), 80.0 (*C*Me_3), 123.2 (*C*(2)), 126.5, 128.4, 126.9 (*o*,*m*,*p*-*Ph*), 145.8 (*i*-*Ph*), 147.5 (*C*(3)), 166.1 (*C*(1)); *m*/*z* (ESI^+) 290 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{18}H_{28}NO_2^+$ ($[M+H]^+$) requires 290.2115; found 290.2117.

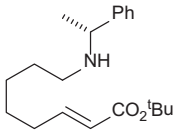
*4.2.8. tert-Butyl (E,R)-7-[N-(α-methylbenzyl)amino]hept-2-enoate **29**.*



Step 1: $NaBH(OAc)_3$ (3.31 g, 15.6 mmol) was added to a solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (3.30 g, 15.6 mmol) and **26** (2.06 g, 10.4 mmol, >99:1 dr [(*E*)/(*Z*)]) in THF (40 mL) and the resultant solution was stirred at rt for 16 h. 1.0 M aq NaOH (10 mL) was then added and the aqueous layer was extracted with EtOAc (40 mL). The combined organic layers were then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 15:1) gave *tert*-butyl (*E*,*R*)-7-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hept-2-enoate as a pale yellow oil (3.22 g, 79%, >99:1 dr [(*E*)/(*Z*)]); $C_{26}H_{35}NO_2$ requires C, 79.35; H, 9.0; N, 3.6%; found C, 79.2; H, 8.6; N, 3.5%; $[\alpha]_D^{21}$ +18.9 (*c* 1.2 in $CHCl_3$); ν_{max} (film) 1715 (C=O); δ_H (400 MHz, $CDCl_3$) 1.39 (3H, d, *J* 6.8, C(α)*Me*), 1.41–1.49 (4H, m, C(5)H_2, C(6)H_2), 1.51 (9H, s, CMe_3), 2.00–2.06 (2H, app q, *J* 6.9, C(4)H_2), 2.31–2.40 (1H, m, C(7)H_A), 2.48–2.57 (1H, m, C(7)H_B), 3.51 (1H, d, *J* 14.0, NC$H_A$$H_B$Ph), 3.59 (1H, d, *J* 14.0, NCH$_A$$H_B$Ph), 3.93 (1H, q, *J* 6.8, C(α)*H*), 5.69 (1H, d, *J* 15.6, C(2)*H*), 6.82 (1H, dt, *J* 15.6, 6.9, C(3)*H*), 7.22–7.43 (10H, m, 2×*Ph*); δ_C (100 MHz, $CDCl_3$) 14.8 (C(α)*Me*), 25.6, 26.9 (*C*(5), *C*(6)), 28.2 (CMe_3), 31.7 (*C*(4)), 48.7 (*C*(7)), 54.4 (NCH_2Ph), 57.7 (*C*(α)), 79.9 (*C*Me_3), 122.9 (*C*(2)), 126.6, 127.9, 128.0, 128.1, 128.5 (*o*,*m*,*p*-*Ph*), 140.9, 143.8 (*i*-*Ph*), 148.0 (*C*(3)), 166.2 (*C*(1)); *m*/*z* (ESI^+) 394 ($[M+H]^+$, 100%).

Step 2: CAN (1.06 g, 1.91 mmol) was added to a solution of *tert*-butyl (*E*,*R*)-7-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hept-2-enoate (250 mg, 0.64 mmol, >99:1 dr [(*E*)/(*Z*)]) in MeCN/H_2O (v/v 5:1, 10 mL) and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then diluted with Et_2O (20 mL), satd aq $NaHCO_3$ was added (20 mL), and stirring was continued for a further 30 min. The aqueous layer was extracted with Et_2O (2×20 mL) and the combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (gradient elution, 0→30% Et_2O in 30–40 °C petrol) gave **29** as a colourless oil (157 mg, 81%, >99:1 dr [(*E*)/(*Z*)]); $[\alpha]_D^{21}$ +64.8 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3382 (N–H), 1714 (C=O), 1652 (C=C); δ_H (400 MHz, $CDCl_3$) 1.36 (3H, d, *J* 6.6, C(α)*Me*), 1.41–1.52 (4H, m, C(5)H_2, C(6)H_2), 1.48 (9H, s, CMe_3), 2.11–2.17 (2H, app q, *J* 6.9, C(4)H_2), 2.38–2.45 (1H, m, C(7)H_A), 2.47–2.49 (1H, m, C(7)H_B), 3.75 (1H, q, *J* 6.6, C(α)*H*), 5.72 (1H, d, *J* 15.6, C(2)*H*), 6.83 (1H, dt, *J* 15.6, 6.9, C(3)*H*), 7.23–7.36 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 24.3 (C(α)*Me*), 25.8 (*C*(5)), 28.1 (CMe_3), 29.8 (*C*(6)), 31.8 (*C*(4)), 47.5 (*C*(7)), 58.4 (*C*(α)), 80.0 (*C*Me_3), 123.2 (*C*(2)), 126.5, 128.4, 126.8 (*o*,*m*,*p*-*Ph*), 145.7 (*i*-*Ph*), 147.6 (*C*(3)), 166.1 (*C*(1)); *m*/*z* (ESI^+) 304 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{19}H_{30}NO_2^+$ ($[M+H]^+$) requires 304.2271; found 304.2283.

*4.2.9. tert-Butyl (E,R)-8-[N-(α-methylbenzyl)amino]oct-2-enoate **30**.*

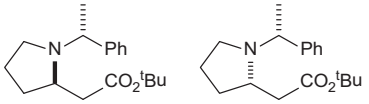


Step 1: $NaBH(OAc)_3$ (134 mg, 0.63 mmol) was added to a solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (133 mg, 0.63 mmol) and

27 (89 mg, 0.42 mmol, 85:15 dr [(*E*)/(*Z*)]) in THF (2 mL) and the resultant solution was stirred at rt for 16 h. 1.0 M aq NaOH (10 mL) was then added and the aqueous layer was extracted with EtOAc (40 mL). The combined organic layers were then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 15:1) gave *tert*-butyl (*E*,*R*)-8-[*N*-benzyl-*N*-(α-methylbenzyl)amino]oct-2-enoate as a colourless oil (120 mg, 63%, 97:3 dr [(*E*)/(*Z*)]); $[\alpha]_D^{20}$ +19.4 (*c* 1.5 in $CHCl_3$); ν_{max} (film) 1714 (C=O); δ_H (400 MHz, $CDCl_3$) 1.21–1.36 (4H, m, C(5)H_2, C(6)H_2), 1.39 (3H, d, *J* 6.8, C(α)*Me*), 1.42–1.48 (2H, m, C(7)H_2), 1.51 (9H, s, CMe_3), 2.07–2.13 (2H, app q, *J* 6.9, C(4)H_2), 2.31–2.38 (1H, m, C(8)H_A), 2.47–2.55 (1H, m, C(8)H_B), 3.52 (1H, d, *J* 14.0, NC$H_A$$H_B$Ph), 3.59 (1H, d, *J* 14.0, NC$H_A$$H_B$Ph), 3.93 (1H, q, *J* 6.8, C(α)*H*), 5.72 (1H, d, *J* 15.6, C(2)*H*), 6.83 (1H, dt, *J* 15.6, 6.9, C(3)*H*), 7.21–7.43 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.9 (C(α)*Me*), 26.7, 27.1, 27.8 (*C*(5), *C*(6), *C*(7)), 28.2 (CMe_3), 32.0 (*C*(4)), 48.9 (*C*(8)), 54.4 (NCH_2Ph), 57.8 (*C*(α)), 79.9 (CMe_3), 122.9 (*C*(2)), 126.6, 127.9, 128.0, 128.1, 128.5 (*o*,*m*,*p*-*Ph*), 141.1, 143.9 (*i*-*Ph*), 148.0 (*C*(3)), 166.2 (*C*(1)); *m*/*z* (ESI$^+$) 408 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{38}NO_2^+$ ([M+H]$^+$) requires 408.2897; found 408.2896.

Step 2: CAN (340 mg, 0.63 mmol) was added to a solution of *tert*-butyl (*E*,*R*)-8-[*N*-benzyl-*N*-(α-methylbenzyl)amino]oct-2-enoate (85 mg, 0.21 mmol, 97:3 dr [(*E*)/(*Z*)]) in MeCN/H_2O (v/v 5:1, 3 mL) and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then diluted with Et_2O (10 mL), satd aq $NaHCO_3$ was added (10 mL), and stirring was continued for a further 30 min. The aqueous layer was extracted with Et_2O (2×10 mL) and the combined organic extracts were dried and concentrated in vacuo. Purification by flash column chromatography (gradient elution, 0→30% Et_2O in 30–40 °C petrol) gave **30** as a colourless oil (55 mg, 70%, >99:1 dr [(*E*)/(*Z*)]); $[\alpha]_D^{23}$ +19.4 (*c* 1.5 in $CHCl_3$); ν_{max} (film) 3422 (N–H), 1714 (C=O), 1653 (C=C); δ_H (400 MHz, $CDCl_3$) 1.25–1.46 (6H, m, C(5)H_2, C(6)H_2, C(7)H_2), 1.39 (3H, d, *J* 6.7, C(α)*Me*), 1.51 (9H, s, *CMe*$_3$), 2.11–2.17 (2H, m, C(4)H_2), 2.37–2.44 (1H, m, C(8)H_A), 2.45–2.53 (1H, m, C(8)H_B), 3.75 (1H, q, *J* 6.7, C(α)*H*), 5.72 (1H, d, *J* 15.6, C(2)*H*), 6.83 (1H, dt, *J* 15.6, 6.9, C(3)*H*), 7.21–7.36 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 24.3 (C(α)*Me*), 26.9, 27.9 (*C*(5), *C*(6)), 28.1 (CMe_3), 29.8 (*C*(7)), 31.9 (*C*(4)), 47.7 (*C*(8)), 58.4 (*C*(α)), 80.0 (*C*Me$_3$), 123.0 (*C*(2)), 126.5, 126.8, 128.4 (*o*,*m*,*p*-*Ph*), 145.7 (*i*-*Ph*), 147.9 (*C*(3)), 166.1 (*C*(1)); *m*/*z* (ESI$^+$) 318 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{32}NO_2^+$ ([M+H]$^+$) requires 318.2428; found 318.2426.

*4.2.10. tert-Butyl (R,R)- and (2′S,αR)-2-[N(1′)-(α-methylbenzyl)pyrrolidin-2′-yl]acetate **31** and **32**.*



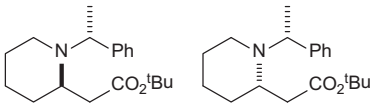
31 **32**

BuLi (0.14 mL, 0.22 mmol) was added dropwise to a solution of **28** (63 mg, 0.22 mmol, >99:1 dr [(*E*)/(*Z*)]) in THF (2 mL) at −78 °C and the resultant mixture was stirred for 2 h at −78 °C. Satd aq NH_4Cl (1 mL) was then added and the aqueous layer was extracted with Et_2O (2×5 mL). The combined organic extracts were then dried and concentrated in vacuo to give a 75:25 mixture of **31** and **32**. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave a 75:25 mixture of **31**[43] and **32** as a colourless oil (59 mg, 93%).

Data for mixture: *m*/*z* (ESI$^+$) 290 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{28}NO_2^+$ ([M+H]$^+$) requires 290.2115; found 290.2119.

Data for **32**: δ_H (400 MHz, $CDCl_3$) 1.38 (3H, d, *J* 6.7, C(α)*Me*), 1.41 (9H, s, C*Me*$_3$), 1.54–1.78 (4H, m, C(3′)H_2, C(4′)H_2), 2.04 (1H, dd, *J* 14.3, 9.8, C(2)H_A), 2.23 (1H, dd, *J* 14.3, 3.3, C(2)H_B), 2.45–2.53 (1H, m, C(5′)H_A), 2.68–2.75 (1H, m, C(5′)H_B), 3.24–3.31 (1H, m, C(2′)*H*), 3.73 (1H, q, *J* 6.7, C(α)*H*), 7.20–7.40 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.7 (C(α)*Me*), 22.8 (*C*(4′)), 28.0 (C*Me*$_3$), 30.7 (*C*(3′)), 40.5 (*C*(2)), 49.3 (*C*(5′)), 58.0 (*C*(2′)), 60.0 (*C*(α)), 80.0 (*C*Me$_3$), 126.8 (*p*-*Ph*), 127.6, 128.1 (*o*,*m*-*Ph*), 145.1 (*i*-*Ph*), 172.1 (*C*(1)).

*4.2.11. tert-Butyl (R,R)- and (2′S,αR)-2-[N(1′)-(α-methylbenzyl)piperidin-2′-yl]acetate **33** and **34**.*



33 **34**

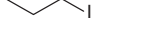
Method A: BuLi (0.21 mL, 0.52 mmol) was added dropwise to a solution of **29** (157 mg, 0.520 mmol, >99:1 dr [(*E*)/(*Z*)]) in THF (5 mL) at −78 °C and the resultant mixture was stirred for 2 h at −78 °C. Satd aq NH_4Cl (1 mL) was then added and the aqueous layer was extracted with Et_2O (2×5 mL). The combined organic extracts were then dried and concentrated in vacuo to give a 50:50 mixture of **33** and **34**. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave **33** as a pale yellow oil (23 mg, 15%, >99:1 dr), and **34** as a pale yellow oil (50 mg, 32%, >99:1 dr).

Data for **33**: $[\alpha]_D^{22}$ +7.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2932 (C–H), 1727 (C=O); δ_H (400 MHz, $CDCl_3$) 1.23–1.78 (6H, m, C(3′)H_2, C(4′)H_2, C(5′)H_2), 1.35 (3H, d, *J* 6.5, C(α)*Me*), 1.40 (9H, s, C*Me*$_3$), 2.25–2.42 (1H, m, C(2)H_A), 2.48–2.69 (3H, m, C(2)H_B, C(6′)H_2), 3.05–3.09 (1H, m, C(2′)*H*), 3.82 (1H, q, *J* 6.5, C(α)*H*), 7.19–7.39 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.2, 25.7, 29.0 (*C*(3′), *C*(4′), *C*(5′)), 21.2 (C(α)*Me*), 28.0 (C*Me*$_3$), 33.8 (*C*(2)), 43.5 (*C*(6′)), 53.0 (*C*(2′)), 59.0 (*C*(α)), 79.9 (*C*Me$_3$), 126.6 (*p*-*Ph*), 127.5, 128.1 (*o*,*m*-*Ph*), 144.5 (*i*-*Ph*), 172.4 (*C*(1)); *m*/*z* (ESI$^+$) 304 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{30}NO_2^+$ ([M+H]$^+$) requires 304.2271; found 304.2283.

Data for **34**: $[\alpha]_D^{22}$ +31.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1728 (C=O); δ_H (400 MHz, $CDCl_3$) 1.31 (3H, d, *J* 6.6, C(α)*Me*) 1.35–1.65 (5H, m, C(3′)H_A, C(4′)H_2, C(5′)H_2), 1.47 (9H, s, C*Me*$_3$), 1.72–1.82 (1H, m, C(3′)H_B), 2.14–2.22 (1H, m, C(6′)H_A), 2.26–2.32 (1H, m, C(6′)H_B), 2.40–2.54 (2H, m, C(2)H_2), 3.45–3.55 (1H, m, C(2′)*H*), 3.67 (1H, q, *J* 6.6, C(α)*H*), 7.19–7.40 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.8 (C(α)*Me*), 20.8 (*C*(5′)), 25.9 (*C*(4′)), 28.1 (C*Me*$_3$), 30.2 (*C*(3′)), 33.3 (*C*(2)), 45.2 (*C*(6′)), 52.6 (*C*(2′)), 59.4 (*C*(α)), 80.2 (*C*Me$_3$), 126.5 (*p*-*Ph*), 127.3, 128.1 (*o*,*m*-*Ph*), 146.3 (*i*-*Ph*), 172.3 (*C*(1)); *m*/*z* (ESI$^+$) 304 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{30}NO_2^+$ ([M+H]$^+$) requires 304.2271; found 304.2278.

Method B: Wilkinson's catalyst (7 mg, 0.083 mmol) was added to a vigorously stirred solution of **78** (500 mg, 1.66 mmol, >99:1 dr) in EtOAc (5 mL) and the resultant mixture was placed under an atmosphere of hydrogen (4 atm) and stirred for 12 h. The reaction mixture was then concentrated in vacuo. Purification via flash column chromatography (eluent pentane/Et_2O, 20:1) gave **33** as a colourless oil (462 mg, 92%, >99:1 dr); $[\alpha]_D^{22}$ +6.8 (*c* 1.0 in $CHCl_3$).

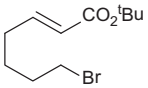
*4.2.12. tert-Butyl (E)-7-iodohept-2-enoate **40**.*



Imidazole (153 mg, 2.25 mmol), PPh_3 (472 mg, 1.80 mmol) and I_2 (457 mg, 1.80 mmol) were added to a solution of **23** (300 mg, 1.50 mmol, >99:1 dr [(*E*)/(*Z*)]) in PhMe/MeCN (v/v 4:1, 10 mL). The resultant mixture was stirred for 2 h at 65 °C and was then allowed to cool to rt. The reaction mixture was diluted with Et_2O (50 mL) and was sequentially washed with satd aq $Na_2S_2O_3$ (20 mL), H_2O (10 mL) and brine (10 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C

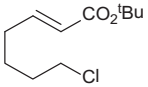
petrol/Et_2O, 10:1) gave **40** as a colourless oil (435 mg, 94%, >99:1 dr [(*E*)/(*Z*)]);[44] δ_H (400 MHz, $CDCl_3$) 1.49 (9H, s, CMe_3), 1.52–1.62 (2H, m, C(5)H_2), 1.81–1.90 (2H, m, C(6)H_2), 2.17–2.25 (2H, m, C(4)H_2), 3.20 (2H, t, *J* 6.9, C(7)H_2), 5.76 (1H, dt, *J* 15.7, 1.7, C(2)*H*), 6.83 (1H, dt, *J* 15.7, 6.8, C(3)*H*).

4.2.13. *tert-Butyl (E)-7-bromohept-2-enoate* ***41***.



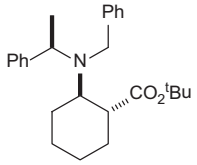
Polystyrene supported PPh_3 (1.0 mmol/g, 500 mg, 0.50 mmol) was added to a solution of **23** (50 mg, 0.50 mmol, >99:1 dr [(*E*)/(*Z*)]) in CH_2Cl_2 (5 mL) at 0 °C. A solution of CBr_4 (166 mg, 0.50 mmol) in CH_2Cl_2 (5 mL) was then added and the reaction mixture was stirred at rt for 1 h then filtered, washed with H_2O (10 mL), dried, and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 50:1) gave **41** as a colourless oil (121 mg, 92%, >99:1 dr [(*E*)/(*Z*)]);[22a] δ_H (400 MHz, $CDCl_3$) 1.49 (9H, s, CMe_3), 1.57–1.66 (2H, m, C(5)H_2), 1.85–1.93 (2H, m, C(6)H_2), 2.18–2.25 (2H, m, C(4)H_2), 3.42 (2H, t, *J* 6.7, C(7)H_2), 5.76 (1H, dt, *J* 15.6, 1.5, C(2)*H*), 6.84 (1H, dt, *J* 15.6, 6.9, C(3)*H*).

4.2.14. *tert-Butyl (E)-7-chlorohept-2-enoate* ***42***.



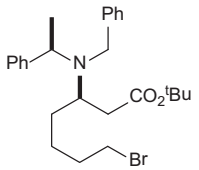
$SOCl_2$ (63 mg, 0.53 mmol) was added to pyridine (0.5 mL) at rt then **23** (75 mg, 0.38 mmol, >99:1 dr [(*E*)/(*Z*)]) was added and the resultant mixture was heated at 50 °C for 6 h. The reaction mixture was then allowed to cool to rt, CH_2Cl_2 (20 mL) and satd aq K_2CO_3 (10 mL) were added, and the aqueous layer was extracted with CH_2Cl_2 (20 mL). The combined organic extracts were sequentially washed with satd aq $CuSO_4$ (2×15 mL) and H_2O (15 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 50:1) gave **42** as a colourless oil (73 mg, 88%, >99:1 dr [(*E*)/(*Z*)]);[12a] δ_H (400 MHz, $CDCl_3$) 1.49 (9H, s, CMe_3), 1.57–1.67 (2H, m, C(5)H_2), 1.72–1.85 (2H, m, C(6)H_2), 2.18–2.25 (2H, m, C(4)H_2), 3.54 (2H, t, *J* 6.5, C(7)H_2), 5.75 (1H, dt, *J* 15.6, 1.6, C(2)*H*), 6.83 (1H, dt, *J* 15.6, 6.9, C(3)*H*).

4.2.15. *tert-Butyl (R,R,R)-2-[N-benzyl-N-(α-methylbenzyl)amino]cyclohexane-1-carboxylate* ***44***.



Following the *general procedure*, **40** (150 mg, 0.484 mmol, >99:1 dr [(*E*)/(*Z*)]), (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (102 mg, 0.484 mmol) and BuLi (0.30 mL, 0.48 mmol) in THF (5 mL) were reacted to give, after purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 50:1), **44** as a pale yellow oil (110 mg, 58%, >99:1 dr);[52] $[\alpha]_D^{20}$ −21.6 (*c* 0.6 in $CHCl_3$); {lit.[45] $[\alpha]_D^{25}$ −29.6 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.25–1.85 (8H, m, C(3)H_2, C(4)H_2, C(5)H_2, C(6)H_2), 1.40 (3H, d, *J* 6.9, C(α)*Me*), 1.49 (9H, s, CMe_3), 2.24 (1H, td, *J* 11.5, 3.7, C(2)*H*), 3.06 (1H, td, *J* 11.5, 3.3, C(1)*H*), 3.72 (1H, d, *J* 14.4, NC$H_A$$H_B$Ph), 3.77 (1H, d, *J* 14.4, NCH$_A$$H_B$Ph), 4.10 (1H, q, *J* 6.9, C(α)*H*), 7.18–7.36 (10H, m, *Ph*).

4.2.16. *tert-Butyl (R,R)-3-[N-benzyl-N-(α-methylbenzyl)amino]-7-bromoheptanoate* ***45***.

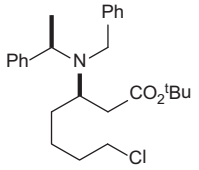


Following the *general procedure*, **41** (75 mg, 0.286 mmol, >99:1 dr [(*E*)/(*Z*)]), (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (124 mg, 0.456 mmol) and BuLi (0.28 mL, 0.44 mmol) in THF (4 mL) were reacted to give, after purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 30:1), a 56:44 mixture of **44** (>99:1 dr) and **45** (>99:1 dr), respectively, as a colourless oil (89 mg).[45]

Data for mixture: *m*/*z* (ESI^+) 394 ($[M+H]^+$ for **44**, 100%), 476 ($[M+H]^+$ for **45**, 20%).

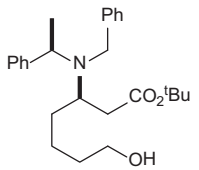
Data for **45**: δ_H (400 MHz, $CDCl_3$) 1.00–1.85 (6H, m, C(4)H_2, C(5)H_2, C(6)H_2), 1.36 (3H, d, *J* 7.0, C(α)*Me*), 1.40 (9H, s, CMe_3), 1.89 (1H, dd, *J* 14.7, 9.6, C(2)H_A), 1.99 (1H, dd, *J* 14.7, 3.2, C(2)H_B), 3.23–3.35 (1H, m, C(3)*H*), 3.40 (2H, app t, *J* 6.4, C(7)H_2), 3.51 (1H, d, *J* 15.0, NC$H_A$$H_B$Ph), 3.78–3.83 (1H, m, NCH$_A$$H_B$Ph), 3.84 (1H, q, *J* 7.0, C(α)*H*), 7.18–7.39 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.6 (C(α)*Me*), 28.1 (CMe_3), 25.5, 32.4, 32.6 (*C*(4), *C*(5), *C*(6)), 34.0 (*C*(7)), 37.5 (*C*(2)), 50.1 (NCH_2Ph), 53.7 (*C*(3)), 58.5 (*C*(α)), 80.0 (*C*Me_3), 126.5, 127.0 (*p*-*Ph*), 128.0, 128.1, 128.3, 128.9 (*o*,*m*-*Ph*), 141.9, 144.7 (*i*-*Ph*), 172.1 (*C*(1)).

4.2.17. *tert-Butyl (R,R)-3-[N-benzyl-N-(α-methylbenzyl)amino]-7-chloroheptanoate* ***46***.



Following the *general procedure*, **42** (80 mg, 0.366 mmol, >99:1 dr [(*E*)/(*Z*)]), (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (124 mg, 0.586 mmol) and BuLi (0.36 mL, 0.57 mmol) in THF (4.0 mL) were reacted to give **46** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 25:1) gave **46** as a colourless oil (120 mg, 76%, >99:1 dr); $[\alpha]_D^{21}$ +7.2 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1724 (C=O); δ_H (400 MHz, $CDCl_3$) 1.24–1.81 (6H, m, C(4)H_2, C(5)H_2, C(6)H_2), 1.33 (3H, d, *J* 7.0, C(α)*Me*), 1.41 (9H, s, CMe_3), 1.89 (1H, dd, *J* 14.7, 9.6, C(2)H_A), 1.99 (1H, dd, *J* 14.7, 3.2, C(2)H_B), 3.23–3.35 (1H, m, C(3)*H*), 3.49–3.53 (1H, m, NC$H_A$$H_B$Ph), 3.52 (2H, t, *J* 6.5, C(7)H_2), 3.81 (1H, d, *J* 14.9, NCH$_A$$H_B$Ph), 3.84 (1H, q, *J* 7.0, C(α)*H*), 7.23–7.47 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.6 (C(α)*Me*), 28.1 (CMe_3), 24.1, 32.4, 32.7 (*C*(4), *C*(5), *C*(6)), 37.5 (*C*(2)), 45.1 (*C*(7)), 50.1 (NCH_2Ph), 53.7 (*C*(3)), 58.5 (*C*(α)), 80.0 (*C*Me_3), 126, 127.0 (*p*-*Ph*), 127.9, 128.1, 128.2, 128.3 (*o*,*m*-*Ph*), 141.9, 143.0 (*i*-*Ph*), 172.1 (*C*(1)); *m*/*z* (ESI^+) 430 ($[M(^{35}Cl)+H]^+$, 100%); HRMS (ESI^+) $C_{26}H_{37}{}^{35}ClNO_2{}^+$ ($[M(^{35}Cl)+H]^+$) requires 430.2507; found 430.2507.

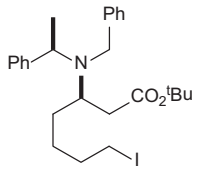
4.2.18. *tert-Butyl (R,R)-3-[N-benzyl-N-(α-methylbenzyl)amino]-7-hydroxyheptanoate* ***47***.



Following the *general procedure*, **23** (243 mg, 1.22 mmol, >99:1 dr [(*E*)/(*Z*)]), (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (667 mg,

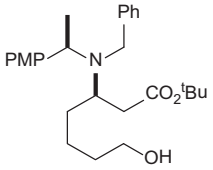
3.16 mmol) and BuLi (1.24 mL, 3.11 mmol) in THF (20 mL) were reacted to give **47** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 1:0; increased to 30–40 °C petrol/Et_2O, 2:1) gave **47** as a colourless oil (330 mg, 66%, >99:1 dr); $[\alpha]_D^{21}$ +9.5 (*c* 1.1 in $CHCl_3$); {lit.[25] for enantiomer $[\alpha]_D^{25}$ −12.6 (*c* 1.2 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.21–1.69 (6H, m, C(4)H_2, C(5)H_2, C(6)H_2), 1.33 (3H, d, *J* 7.0, C(α)*Me*), 1.40 (9H, s, CMe_3), 1.88 (1H, dd, *J* 14.6, 9.5, C(2)H_A), 1.97 (1H, dd, *J* 14.6, 3.4, C(2)H_B), 3.27–3.34 (1H, m, C(3)*H*), 3.49 (1H, d, *J* 14.9, NC$H_A$$H_B$Ph), 3.61 (2H, t, *J* 6.4, C(7)H_2), 3.79 (1H, d, *J* 14.9, NCH$_A$$H_B$Ph), 3.82 (1H, q, *J* 7.0, C(α)*H*), 7.22–7.45 (10H, m, *Ph*).

*4.2.19. tert-Butyl (R,R)-3-[N-benzyl-N-(α-methylbenzyl)amino]-7-iodoheptanoate **48**.*



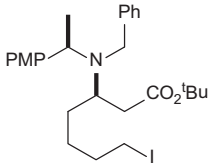
I_2 (232 mg, 0.91 mmol) was added to a stirred solution of imidazole (62 mg, 0.91 mmol), PPh_3 (239 mg, 0.91 mmol) and **47** (75 mg, 0.18 mmol, >99:1 dr) in PhMe/MeCN (v/v 4:1, 7.5 mL) and the resultant solution was stirred at 65 °C for 16 h. The reaction mixture was then allowed to cool to rt, diluted with Et_2O (10 mL), then sequentially washed with satd aq $Na_2S_2O_3$ (15 mL), H_2O (15 mL) and brine (15 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (gradient elution, 0→4% Et_2O in 30–40 °C petrol) gave **48** as a pale yellow oil (85 mg, 85%, >99:1 dr); $[\alpha]_D^{23}$ +1.49 (*c* 1.6 in $CHCl_3$); ν_{max} (film) 1724 (C=O); δ_H (500 MHz, $CDCl_3$) 1.32–1.56 (3H, m, C(4)H_2, C(5)H_A), 1.37 (3H, d, *J* 7.0, C(α)*Me*), 1.43 (9H, s, CMe_3), 1.69–1.79 (3H, m, C(5)H_B, C(6)H_2), 1.91 (1H, dd, *J* 14.6, 9.7, C(2)H_A), 2.01 (1H, dd, *J* 14.6, 3.1, C(2)H_B), 3.15–3.20 (2H, m, C(7)H_2), 3.28–3.34 (1H, m, C(3)*H*), 3.53 (1H, d, *J* 15.0, NC$H_A$$H_B$Ph), 3.82 (1H, d, *J* 15.0, NCH$_A$$H_B$Ph), 3.82 (1H, q, *J* 7.0, C(α)*H*), 7.26–7.48 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 7.2 (*C*(7)), 20.7 (C(α)*Me*), 27.9 (*C*(4)), 28.1 (CMe_3), 32.4 (*C*(5)), 33.3 (*C*(6)), 37.6 (*C*(2)), 50.2 (NCH_2Ph), 53.8 (*C*(3)), 58.6 (*C*(α)), 80.1 (*C*Me$_3$), 126.6, 127.0 (*p-Ph*), 127.9, 128.1, 128.2, 128.3 (*o,m-Ph*), 142.0, 143.1 (*i-Ph*), 172.1 (*C*(1)); *m/z* (ESI$^+$) 522 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{37}INO_2^+$ ([M+H]$^+$) requires 522.1863; found 522.1869.

*4.2.20. tert-Butyl (R,R)-3-[N-benzyl-N-(α-methyl-p-methoxybenzyl) amino]-7-hydroxyheptanoate **52**.*



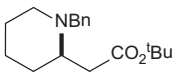
Following the *general procedure*, **23** (500 mg, 2.69 mmol, >99:1 dr [(*E*)/(*Z*)]), (*R*)-*N*-benzyl-*N*-(α-methyl-*p*-methoxybenzyl)amine (1.69 g, 6.99 mmol) and BuLi (2.74 mL, 6.85 mmol) in THF (15 mL) were reacted to give **52** in >99:1 dr. Purification via flash column chromatography (gradient elution, 0→30% Et_2O in 30–40 °C petrol) gave **52** as a colourless oil (770 mg, 76%, >99:1 dr); $[\alpha]_D^{23}$ +28.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3427 (O–H), 1722 (C=O); δ_H (400 MHz, $CDCl_3$) 1.31–1.40 (1H, m, C(4)H_A), 1.35 (3H, d, *J* 6.9, C(α)*Me*), 1.41 (9H, s, CMe_3), 1.48–1.57 (1H, m, C(4)H_B), 1.63–1.73 (1H, m, C(5)H_A), 1.84–1.98 (5H, m, C(2)H_2, C(5)H_B, C(6)H_2), 3.32–3.39 (1H, m, C(3)*H*), 3.48 (1H, d, *J* 15.0, NC$H_A$$H_B$Ph), 3.60 (2H, t, *J* 6.4, C(7)H_2), 3.77–3.82 (2H, m, NCH$_A$$H_B$Ph, C(α)*H*), 3.81 (3H, s, O*Me*), 6.87 (2H, d, *J* 7.7, *Ar*), 7.22–7.28 (3H, m, *Ph*), 7.35–7.38 (2H, m, *Ph*), 7.43 (2H, d, *J* 7.7, *Ar*); δ_C (100 MHz, $CDCl_3$) 20.6 (C(α)*Me*), 28.1 (CMe_3), 29.7, 30.0, 30.4 (*C*(4), *C*(5), *C*(6)), 37.5 (*C*(2)), 50.1 (NCH_2Ph), 53.0 (*C*(3)), 55.2 (O*Me*), 57.3 (*C*(α)), 62.6 (*C*(7)), 80.2 (*C*Me$_3$), 113.5 (*Ar*), 126.7 (*p-Ph*), 128.2, 128.3, 128.9 (*o,m-Ph*, *Ar*), 134.8, 141.7 (*i-Ph*, *Ar*), 158.6 (*Ar*), 172.5 (*C*(1)); *m/z* (ESI$^+$) 442 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{40}NO_4^+$ ([M+H]$^+$) requires 442.2952; found 442.2950.

*4.2.21. tert-Butyl (3R,αR)-3-[N-benzyl-N-(α-methyl-p-methoxybenzyl)amino]-7-iodoheptanoate **53**.*



I_2 (860 mg, 3.39 mmol) was added to a stirred solution of imidazole (231 mg, 3.39 mmol), PPh_3 (890 mg, 3.39 mmol) and **52** (300 mg, 0.679 mmol, >99:1 dr) in PhMe/MeCN (v/v 4:1, 25 mL) and the resultant solution was stirred at 65 °C for 16 h. The reaction mixture was then allowed to cool to rt, diluted with Et_2O (10 mL), then sequentially washed with satd aq $Na_2S_2O_3$ (15 mL), H_2O (15 mL) and brine (15 mL), before being dried and concentrated in vacuo. Purification via flash column chromatography (gradient elution, 0→4% Et_2O in 30–40 °C petrol) gave **53** as a pale yellow oil (340 mg, 91%, >99:1 dr); $[\alpha]_D^{23}$ +8.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1723 (C=O); δ_H (400 MHz, $CDCl_3$) 1.32 (3H, d, *J* 7.0, C(α)*Me*), 1.34–1.51 (3H, m, C(4)H_2, C(5)H_A), 1.42 (9H, s, CMe_3), 1.68–1.80 (3H, m, C(5)H_B, C(6)H_2), 1.87 (1H, dd, *J* 14.7, 9.8, C(2)H_A), 1.98 (1H, dd, *J* 14.7, 3.0, C(2)H_B), 3.15–3.21 (2H, m, C(7)H_2), 3.25–3.32 (1H, m, C(3)*H*), 3.47 (1H, d, *J* 15.0, NC$H_A$$H_B$Ph), 3.75–3.82 (2H, m, NCH$_A$$H_B$Ph, C(α)*H*), 3.81 (3H, s, O*Me*), 6.86 (2H, d, *J* 7.9, *Ar*), 7.22–7.28 (3H, m, *Ph*), 7.35–7.38 (2H, m, *Ph*), 7.43 (2H, d, *J* 7.9, *Ar*); δ_C (100 MHz, $CDCl_3$) 7.2 (*C*(7)), 20.8 (C(α)*Me*), 27.9 (*C*(4)), 28.1 (CMe_3), 32.4 (*C*(5)), 33.3 (*C*(6)), 37.6 (*C*(2)), 50.0 (NCH_2Ph), 53.4 (*C*(3)), 55.2 (O*Me*), 57.6 (*C*(α)), 80.1 (*C*Me$_3$), 113.5 (*Ar*), 126.6 (*p-Ph*), 128.1, 128.3, 128.9 (*o,m-Ph*, *Ar*), 135.1, 141.9 (*i-Ph*, *Ar*), 158.6 (*Ar*), 172.2 (*C*(1)); *m/z* (ESI$^+$) 552 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{39}INO_3^+$ ([M+H]$^+$) requires 552.1969; found 522.1975.

*4.2.22. tert-Butyl (R)-2-[N(1′)-benzylpiperidin-2′-yl]acetate **49**.*



Method A: A solution of **48** (65 mg, 0.125 mmol) and $AgBF_4$ (37 mg, 0.19 mmol) in MeCN (15 mL) was heated at 80 °C for 16 h. The reaction mixture was then diluted with Et_2O (20 mL) and the resultant solution was washed with satd aq $NaHCO_3$ (20 mL), then dried and concentrated in vacuo. The residue was then filtered through Celite (eluent Et_2O) and the filtrate was concentrated in vacuo. Purification via flash column chromatography (gradient elution, 0→10% Et_2O in 30–40 °C petrol) gave **49** as a colourless oil (21 mg, 55%, >99:1 er[26]), *tert*-butyl (*R*,*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-6-enoate **50** as a colourless oil (16 mg, 33%, >99:1 dr), and (*RS*)-*N*-α-methylbenzyl acetamide **17** as a colourless oil (10 mg, 49%).

Data for **49**: $C_{18}H_{27}NO_2$ requires C, 74.7; H, 9.4; N, 4.8%; found: C, 74.4; H, 9.3; N, 4.6%; $[\alpha]_D^{23}$ +18.6 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1729 (C=O); δ_H (400 MHz, $CDCl_3$) 1.35–1.56 (4H, m, C(3′)H_A, C(4′)H_A, C(5′)H_2), 1.45 (9H, s, CMe_3), 1.59–1.67 (1H, m, C(4′)H_B), 2.13–2.20 (2H, m, C(3′)H_B, C(6′)H_A), 2.34 (1H, dd, *J* 14.5, 8.0, C(2)H_A), 2.58–2.69 (2H, m, C(2)H_B, C(6′)H_B), 2.91–2.97 (1H, m, C(2′)*H*), 3.36 (1H, d, *J* 13.5, NC$H_A$$H_B$Ph), 3.80 (1H, d, *J* 13.5, NCH$_A$$H_B$Ph), 7.21–7.41 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 22.3 (*C*(5′)), 25.3 (*C*(4′)), 28.1 (CMe_3), 31.0 (*C*(3′)), 37.4 (*C*(2)), 50.7 (*C*(6′)), 57.7 (*C*(2′)), 58.6

(NCH_2Ph), 80.3 (CMe_3), 126.7 (*p-Ph*), 128.1, 128.8 (*o,m-Ph*), 139.6 (*i-Ph*), 172.3 (*C*(1)); *m*/*z* (ESI^+) 290 ($[M+H]^+$, 100%), 234 ($[M-C_4H_8]^+$, 10%).

Data for **50**: $[\alpha]_D^{26}$ +8.1 (*c* 0.9 in $CHCl_3$); ν_{max} (film) 1725 (C=O), 1641 (C=C); δ_H (400 MHz, $CDCl_3$) 1.35 (3H, d, *J* 7.0, C(α)*Me*), 1.41 (9H, s, CMe_3), 1.46–1.60 (2H, m, C(4)H_2), 1.86–1.90 (2H, m, C(2)H_2), 2.11–2.19 (1H, m, C(5)H_A), 2.35–2.45 (1H, m, C(5)H_B), 3.32–3.40 (1H, m, C(3)*H*), 3.49 (1H, d, *J* 15.0, NCH_AH_BPh), 3.79–3.82 (1H, m, NCH_AH_BPh), 3.82 (1H, q, *J* 7.0, C(α)*H*), 4.92–4.96 (1H, m, C(7)H_A), 4.99–5.05 (1H, m, C(7)H_B), 5.75–5.86 (1H, m, C(6)*H*), 7.24–7.46 (10H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 20.4 (C(α)*Me*), 28.0 (CMe_3), 31.2 (*C*(5)), 32.8 (*C*(4)), 37.7 (*C*(2)), 50.0 (NCH_2Ph), 53.2 (*C*(3)), 58.0 (*C*(α)), 80.0 (CMe_3), 114.4 (*C*(7)), 126.6, 126.9 (*p*-Ph), 127.9, 128.1, 128.3, 129.0 (*o,m-Ph*), 138.9 (*C*(6)), 141.7, 142.6 (*i-Ph*), 172.1 (*C*(1)); *m*/*z* (CI^+) 394 ($[M+H]^+$, 100%); HRMS (CI^+) $C_{26}H_{35}NO_2^+$ ($[M+H]^+$) requires 394.2741; found 394.2742.

Method B: A solution of **53** (50 mg, 0.091 mmol) and $AgBF_4$ (26 mg, 0.14 mmol) in MeCN (5 mL) was heated at 80 °C for 16 h. The reaction mixture was then diluted with Et_2O (20 mL) and the resultant solution was washed with satd aq $NaHCO_3$ (20 mL) then dried and concentrated in vacuo. The residue was then filtered through Celite (eluent Et_2O) and the filtrate was concentrated in vacuo. Purification via flash column chromatography (gradient elution, 0→10% Et_2O in 30–40 °C petrol) gave **49** as a colourless oil (22 mg, 84%, >99:1 er[26]); $[\alpha]_D^{23}$ +20.9 (*c* 1.0 in $CHCl_3$).

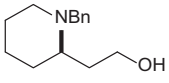
Method C: A solution of **53** (1.37 g, 2.48 mmol) in MeCN (140 mL) was heated at 80 °C for 16 h. The reaction mixture was then diluted with Et_2O (20 mL) and the resultant solution was washed with satd aq $NaHCO_3$ (20 mL) then dried and concentrated in vacuo. The residue was then filtered through Celite (eluent Et_2O) and the filtrate was concentrated in vacuo. Purification via flash column chromatography (gradient elution, 0→10% Et_2O in 30–40 °C petrol) gave **49** as a colourless oil (667 mg, 94%, >99:1 er[26]), and *p*-methoxystyrene **55** as a pale yellow oil (217 mg, 65%).

Data for **49**: $[\alpha]_D^{23}$ +18.6 (*c* 1.0 in $CHCl_3$).

Method D: Imidazole (2.11 g, 31.0 mmol), PPh_3 (8.11 g, 31.0 mmol) and I_2 (7.65 g, 30.1 mmol) were added to a solution of **52** (2.74 g, 6.19 mmol) in MeCN (150 mL). The resultant mixture was stirred at 80 °C for 16 h then filtered and concentrated in vacuo. The residue was dissolved in Et_2O and the resultant solution was sequentially washed with satd aq $Na_2S_2O_3$ (20 mL), H_2O (20 mL) and brine (20 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (gradient elution, 0→10% Et_2O in 30–40 °C petrol) gave **49** as a colourless oil (1.35 g, 75%, >99:1 er[26]), and *p*-methoxystyrene **55** as a pale yellow oil (273 mg, 33%).

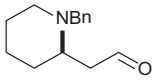
Data for **49**: $[\alpha]_D^{23}$ +22.5 (*c* 1.1 in $CHCl_3$).

4.2.23. *(R)-2-[N(1′)-Benzylpiperidin-2′-yl]ethanol* ***60***.



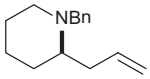
DIBAL-H (1.0 M in THF, 6.05 mL, 6.05 mmol) was added to a stirred solution of **49** (350 mg, 1.21 mmol) in THF (15 mL) at 0 °C. The resultant solution was allowed to warm to rt over 6 h and was then cooled to 0 °C before H_2O (5 mL) was added. The reaction mixture was then allowed to warm to rt, 1.0 M aq KOH (10 mL) was added and the resultant mixture was stirred at rt for 16 h. The aqueous layer was then extracted with Et_2O (2×20 mL) and the combined organic extracts were dried and concentrated in vacuo to give **60** as a colourless oil (263 mg, 99%);[46] $[\alpha]_D^{25}$ +28.6 (*c* 1.0 in $CHCl_3$); {lit.[47] $[\alpha]_D^{23}$ +28.5 (*c* 2.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.32–1.84 (7H, m, C(3′)H_2, C(4′)H_2, C(5′)H_2, C(2)H_A), 1.91–2.00 (1H, m, C(2)H_B), 2.17–2.23 (1H, m, C(6′)H_A), 2.71–2.77 (1H, m, C(2′)*H*), 2.92–2.99 (1H, m, C(6′)H_B), 3.47 (1H, d, *J* 12.9, NCH_AH_BPh), 3.72–3.78 (1H, m, C(1)H_A), 3.90–3.98 (1H, m, C(1)H_B) 4.17 (1H, d, *J* 12.9, NCH_AH_BPh), 5.09 (1H, br s, CH_2OH) 7.23–7.35 (5H, m, *Ph*).

4.2.24. *(R)-2-[N(1′)-Benzylpiperidin-2′-yl]ethanal* ***58***.



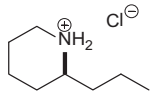
DMSO (0.28 mL, 4.75 mmol) was added to a solution of $(COCl)_2$ (0.21 mL, 2.37 mmol) in CH_2Cl_2 (10 mL) at −78 °C and the resultant solution was stirred at −78 °C for 20 min. A solution of **60** (260 mg, 1.19 mmol) in CH_2Cl_2 (10 mL) was then added via cannula. After a further 20 min, NEt_3 (1.0 mL, 7.12 mmol) was added and the reaction mixture was allowed to warm to rt, stirred for 30 min, then concentrated in vacuo. The residue was partitioned between Et_2O (20 mL) and H_2O (20 mL), the aqueous layer was extracted with Et_2O (2×20 mL), and the combined organic extracts were dried and concentrated in vacuo to give **58** as a colourless oil (258 mg, quant); $[\alpha]_D^{23}$ +8.1 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1721 (C=O); δ_H (500 MHz, $CDCl_3$) 1.41–1.56 (2H, m, C(4′)H_A, C(5′)H_A), 1.56–1.66 (2H, m, C(3′)H_A, C(4′)H_B), 1.68–1.77 (1H, m, C(5′)H_B), 1.81–1.88 (2H, m, C(3′)H_B), 2.17–2.24 (1H, m, C(6′)H_A), 2.64–2.80 (3H, m, C(2)H_2, C(6′)H_B), 3.01–3.07 (1H, m, C(2′)*H*), 3.34 (1H, d, *J* 13.2, NCH_AH_BPh), 3.92 (1H, d, *J* 13.2, NCH_AH_BPh), 7.26–7.38 (5H, m, *Ph*), 9.89 (1H, app s, C(1)*H*); δ_C (125 MHz, $CDCl_3$) 22.9 (*C*(5′)), 24.9 (*C*(4′)), 31.2 (*C*(3′)), 45.6 (*C*(2)), 50.9 (*C*(6′)), 56.0 (*C*(2′)), 58.5 (NCH_2Ph), 127.0 (*p-Ph*), 128.3, 128.8 (*o,m-Ph*), 139.2 (*i-Ph*), 202.4 (*C*(1)); *m*/*z* (FI^+) 217 ($[M]^+$, 100%); HRMS (FI^+) $C_{14}H_{19}NO^+$ ($[M]^+$) requires 217.1461; found 217.1464.

4.2.25. *(R)-N(1)-Benzyl-2-allylpiperidine* ***57***.



^{t}BuOK (116 mg, 1.04 mmol) was added portionwise to a suspension of methyltriphenylphosphonium bromide (412 mg, 1.15 mmol) in THF (6 mL) at 0 °C and the resultant mixture was stirred at rt for 30 min. A solution of **58** (125 mg, 0.58 mmol) in THF (2 mL) was then added dropwise. The reaction mixture was stirred at rt for 16 h then satd aq NH_4Cl (1 mL) was added. The aqueous layer was extracted with Et_2O (3×5 mL) and the combined organic extracts were washed with brine (15 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 15:1) gave **57** as a colourless oil (65 mg, 52%); $[\alpha]_D^{23}$ +9.1 (*c* 0.4 in $CHCl_3$); ν_{max} (film) 1639 (C=C); δ_H (500 MHz, $CDCl_3$) 1.30–1.39 (1H, m, C(4)H_A), 1.45–1.57 (3H, m, C(3)H_A, C(5)H_2), 1.66–1.75 (2H, m, C(3)H_B, C(4)H_B), 2.05–2.12 (1H, m, C(6)H_A), 2.40–2.48 (3H, m, C(1′)H_2, C(2)*H*), 2.79 (1H, td, *J* 8.4, 3.9, C(6)H_B), 3.29 (1H, d, *J* 13.3, NCH_AH_BPh), 4.08 (1H, d, *J* 13.3, NCH_AH_BPh), 5.09–5.15 (2H, m, C(3′)H_2), 5.94 (1H, tdd, *J* 13.6, 10.2, 6.8, C(2′)*H*), 7.26–7.40 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 23.4 (*C*(5)), 25.4 (*C*(4)), 30.4 (*C*(3)), 36.2 (*C*(1′)), 51.7 (*C*(6)), 57.9 (NCH_2Ph), 60.2 (*C*(2)), 116.3 (*C*(3′)), 126.7 (*p-Ph*), 128.1, 129.0 (*o,m-Ph*), 136.0 (*C*(2′)), 139.6 (*i-Ph*); *m*/*z* (ESI^+) 216 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{15}H_{22}N^+$ ($[M+H]^+$) requires 216.1747; found 216.1755.

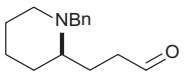
4.2.26. *(S)-2-Propylpiperidine hydrochloride [(S)-coniine hydrochloride]* ***1***·*HCl*.



$Pd(OH)_2/C$ (20% w/w, 40 mg) was added to a degassed solution of **57** (50 mg, 0.23 mmol) in MeOH (3 mL) and the resultant solution was stirred under an atmosphere of H_2 (1 atm) for 48 h. The reaction mixture was then filtered through Celite (eluent MeOH), excess

ethereal HCl was added, and the resultant mixture was concentrated in vacuo. Purification via flash column chromatography (gradient elution, 0→10% MeOH in CH_2Cl_2) gave **1**·HCl as a white solid (30 mg, 82%, >99:1 er); mp 207–209 °C; {lit.[33] mp 214–216 °C}; $[\alpha]_D^{23}$ +9.2 (*c* 0.3 in EtOH) {lit.[34] $[\alpha]_D^{23}$ +9.4 (*c* 0.3 in EtOH)}; δ_H (400 MHz, $CDCl_3$) 0.94 (3H, t, *J* 7.3, C(3′)H_3), 1.36–2.04 (10H, m, C(3)H_2, C(4)H_2, C(5)H_2, C(1′)H_2, C(2′)H_2), 2.75–2.86 (1H, m, C(6)H_A), 2.87–3.00 (1H, m, C(6)H_B), 3.40–3.53 (1H, br m, C(2)*H*), 9.19 (1H, br s, NH_A), 9.49 (1H, br s, NH_B).

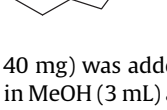
*4.2.27. (R)-3-[N(1′)-Benzylpiperidin-2′-yl]propanal **59**.*



Step 1: ^{t}BuOK (83 mg, 0.74 mmol) was added portionwise to a suspension of methoxymethyltriphenylphosphonium chloride (282 mg, 0.82 mmol) in THF (4 mL) at 0 °C and the resultant mixture was stirred at rt for 30 min. A solution of **58** (89 mg, 0.41 mmol) in THF (2 mL) was then added dropwise. The reaction mixture was stirred at rt for 16 h then satd aq NH_4Cl (1 mL) was added. The aqueous layer was extracted with Et_2O (3×5 mL) and the combined organic extracts were washed with brine (15 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 15:1) gave (*R*)-*N*(1)-benzyl-2-(4′-methoxybut-3′-en-1′-yl)piperidine **61** as a yellow oil (81 mg, 81%, 52:48 dr).

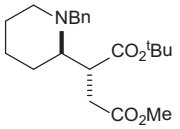
Step 2: A solution of **61** (60 mg, 0.25 mmol, 52:48 dr) in CH_2Cl_2/HCO_2H (v/v 4:1, 5 mL) was stirred for 16 h at rt. $NaHCO_3$ (~200 mg) was then added until pH >11 was achieved. The aqueous layer was then extracted with CH_2Cl_2 (3×15 mL) and the combined organic extracts were dried and concentrated in vacuo to give **59** as a yellow oil (56 mg, quant); $[\alpha]_D^{23}$ +21.1 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1724 (C=O); δ_H (400 MHz, $CDCl_3$) 1.30–1.57 (4H, m, C(3′)H_2, C(5′)H_2), 1.61–1.73 (2H, m, C(4′)H_2), 1.91–1.99 (2H, m, C(3)H_2), 2.05–2.15 (1H, m, C(6′)H_A), 2.37–2.46 (1H, m, C(2′)*H*), 2.47–2.64 (2H, m, C(2)H_2), 2.75–2.83 (1H, m, C(6′)H_B), 3.29 (1H, d, *J* 13.5, NC$H_A$$H_B$Ph), 3.97 (1H, d, *J* 13.5, NC$H_A$$H_B$Ph), 7.22–7.35 (5H, m, *Ph*), 9.78 (1H, app s, C(1)*H*); δ_C (100 MHz, $CDCl_3$) 23.3 (*C*(4′)), 23.7 (*C*(3)), 24.5 (*C*(5′)), 29.4 (*C*(3′)), 51.1 (*C*(2)), 51.1 (*C*(6′)), 57.4 (*C*(2′)), 59.4 (NCH_2Ph), 126.8 (*p-Ph*), 128.2, 128.8 (o,*m-Ph*), 139.5 (*i-Ph*), 202.5 (*C*(1)); *m*/*z* (FI$^+$) 231 ([M]$^+$, 100%); HRMS (FI$^+$) $C_{15}H_{21}NO^+$ ([M]$^+$) requires 231.1618; found 231.1620.

*4.2.28. (R)-Octahydroindolizine hydrochloride [(R)-δ-coniceine hydrochloride] **56**·HCl.*



$Pd(OH)_2$/C (20% w/w, 40 mg) was added to a degassed solution of **59** (90 mg, 0.39 mmol) in MeOH (3 mL) and the resultant solution was stirred under an atmosphere of H_2 (1 atm) for 48 h. The reaction mixture was then filtered through Celite (eluent MeOH), excess ethereal HCl was added to the filtrate, and the resultant mixture was concentrated in vacuo. Purification via flash column chromatography (eluent CH_2Cl_2/MeOH, 8:1) gave **56**·HCl as a white solid (59 mg, 94%, >99:1 er); mp 175 °C; $[\alpha]_D^{23}$ −1.5 (*c* 1.0 in EtOH); ν_{max} (KBr) 3477 (N–H); δ_H (400 MHz, CD_3OD) 1.56–2.35 (10H, m, C(1)H_2, C(2)H_2, C(6)H_2, C(7)H_2, C(8)H_2), 2.92–3.22 (3H, m, C(3)H_A, C(8a)*H*, C(5)H_A), 3.55–3.68 (2H, m, C(3)H_B, C(5)H_B); δ_C (125 MHz, CD_3OD) 20.5, 23.5, 24.4, 29.2, 29.5 (*C*(1), *C*(2), *C*(6), *C*(7), *C*(8)), 52.8, 53.6 (*C*(3), *C*(5)), 68.0 (*C*(8a)); *m*/*z* (ESI$^+$) 126 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_8H_{16}N^+$ ([M+H]$^+$) requires 126.1277; found 126.1278.

*4.2.29. tert-Butyl (R,R)-2-[N(1′)-benzylpiperidin-2′-yl]-4-methoxy-4-oxobutanoate **66**.*



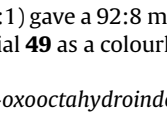
Method A: BuLi (0.26 mL, 0.65 mmol) was added to a stirred solution of HTMP (0.12 mL, 0.70 mmol) in THF (3.0 mL) at −78 °C. After 30 min the reaction mixture was allowed to warm to rt and stirred at rt for a further 10 min, before being cooled back down to −78 °C. A solution of **49** (100 mg, 0.35 mmol) in THF (3.0 mL) at −78 °C was then added. The resultant mixture was stirred for 1 h at −78 °C then methyl bromoacetate (159 mg, 1.04 mmol) was added. The reaction mixture was then allowed to warm to rt over 16 h, satd aq NH_4Cl was added, and the resultant mixture was extracted with EtOAc (2×5 mL). The combined organic extracts were washed with brine (10 mL) then dried and concentrated in vacuo to give **66** in 90:10 dr (70% conv). Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 50:1) gave a 77:23 mixture of **66** (98:2 dr) and recovered starting material **49** as a colourless oil (89 mg).

Data for **66**: δ_H (500 MHz, $CDCl_3$) 1.25–1.58 (5H, m, C(3′)H_2, C(4′)H_A, C(5′)H_2), 1.51 (9H, s, CMe_3), 1.73–1.79 (1H, m, C(4′)H_B), 1.98 (1H, dt, *J* 11.7, 2.5, C(6′)H_A), 2.69–2.74 (1H, m, C(2′)*H*), 2.77–2.81 (2H, m, C(3)H_2), 2.87–2.92 (1H, m, C(6′)H_B), 3.18 (1H, d, *J* 13.5, NC$H_A$$H_B$Ph), 3.57–3.61 (1H, m, C(2)*H*), 3.70 (3H, s, O*Me*), 4.07 (1H, d, *J* 13.5, NC$H_A$$H_B$Ph), 7.25–7.39 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 25.5, 26.8, 28.2 (*C*(3′), *C*(4′), *C*(5′)), 28.1 (CMe_3), 29.2 (*C*(3)), 43.8 (*C*(2)), 51.7 (O*Me*), 53.0 (*C*(6′)), 57.7 (NCH_2Ph), 61.8 (*C*(2′)), 80.9 (CMe_3), 126.8 (*p-Ph*), 128.3, 128.8 (*o*,*m-Ph*), 139.1 (*i-Ph*), 172.7, 173.7 (*C*(1), *C*(4)); *m*/*z* (ESI$^+$) 362 ([M+H]$^+$, 100%), 306 ([M−C_4H_8]$^+$, 50%); HRMS (ESI$^+$) $C_{21}H_{32}NO_4^+$ ([M+H]$^+$) requires 362.2326; found 362.2332.

Method B: LiHMDS (1.0 M in THF, 0.52 mL, 0.52 mmol) was added to a solution of **49** (100 mg, 0.35 mmol) in THF (2.0 mL) at −78 °C and the resultant mixture was stirred at −78 °C for 20 min. Methyl bromoacetate (106 mg, 0.69 mmol) was then added, and the reaction mixture was allowed to warm to rt over 4 h before satd aq NH_4Cl (1.0 mL) was added. The reaction mixture was then extracted with Et_2O (2×20 mL) and the combined organic extracts were sequentially washed with H_2O (20 mL) and brine (20 mL), then dried and concentrated in vacuo give **66** in 86:14 dr (69% conv). Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 50:1) gave an 83:17 mixture of **66** (97:3 dr) and recovered starting material **49** as a colourless oil (72 mg).

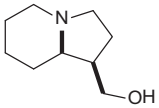
Method C: BuLi (0.33 mL, 0.83 mmol) was added to a stirred solution of ^{i}Pr$_2$NH (0.12 mL, 0.85 mmol) in THF (3.0 mL) at −78 °C. After 30 min the reaction mixture was allowed to warm to rt and stirred at rt for a further 10 min, before being cooled back down to −78 °C. A solution of **49** (123 mg, 0.43 mmol) in THF (3.0 mL) at −78 °C was then added. The resultant mixture was stirred for 1 h at −78 °C then methyl bromoacetate (0.148 mL, 1.28 mmol) was added. The reaction mixture was then allowed to warm to rt over 16 h, satd aq NH_4Cl was added, and the resultant mixture was extracted with EtOAc (2×5 mL). The combined organic extracts were washed with brine (10 mL) then dried and concentrated in vacuo to give **66** in 80:20 dr (85% conv). Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 50:1) gave a 92:8 mixture of **66** (95:5 dr) and recovered starting material **49** as a colourless oil (113 mg).

*4.2.30. tert-Butyl (R,R)-3-oxooctahydroindolizine-1-carboxylate **68**.*



A 77:23 mixture of **66** (98:2 dr) and **49** (89 mg) was dissolved in degassed MeOH (3.0 mL) and $Pd(OH)_2/C$ (20% wt, 20 mg) was added to the resultant solution. The resultant mixture was stirred under H_2 (1 atm) for 48 h then filtered through Celite (eluent MeOH). The filtrate was concentrated in vacuo and the residue was dissolved in $CHCl_3$ (3 mL). The resultant solution was heated at reflux for 16 h then allowed to cool to rt before being concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 1:0; increased to neat Et_2O) gave **68** as a colourless oil (44 mg, 53% from **49**, >99:1 dr); $[\alpha]_D^{23}$ +27.3 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1727 (C=O), 1692 (C=O); δ_H (400 MHz, $CDCl_3$) 1.16–1.51 (3H, m, C(6)H_2, C(8)H_A), 1.45 (9H, s, CMe_3), 1.57–1.64 (1H, m, C(7)H_A), 1.65–1.73 (1H, m, C(8)H_B), 1.88–1.95 (1H, m, C(7)H_B), 2.43 (1H, dd, *J* 17.3, 9.6, C(2)H_A), 2.58–2.67 (1H, m, C(5)H_A), 2.78 (1H, app ddd, *J* 17.3, 8.2, 2.3, C(2)H_B), 3.19–3.26 (1H, m, C(1)*H*), 3.64–3.72 (1H, m, C(8a)*H*), 4.10–4.17 (1H, m, C(5)H_B); δ_C (100 MHz, $CDCl_3$) 23.9, 24.3, 27.6 (*C*(6), *C*(7), *C*(8)), 28.1 (CMe_3), 32.6 (*C*(2)), 40.7 (*C*(5)), 41.0 (*C*(1)), 58.6 (*C*(8a)), 80.9 (*C*Me_3), 170.4, 171.8 (*C*(3), *C*$O_2{}^tBu$); *m/z* (ESI^+) 298 ($[M+MeCN+NH_4]^+$, 100%), 262 ($[M+Na]^+$, 5%); HRMS (ESI^+) $C_{13}H_{22}NO_3^+$ ($[M+H]^+$) requires 240.1609; found 240.1609.

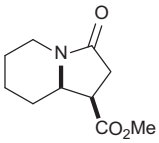
4.2.31. (R,R)-1-(Hydroxymethyl)octahydroindolizine ***62****.*



Method A: $LiAlH_4$ (1.0 M in THF, 1.10 mL, 1.10 mmol) was added to a stirred solution of **68** (44 mg, 0.18 mmol) in THF (4.0 mL) at 0 °C. The resultant mixture was heated at reflux for 16 h, then cooled to 0 °C. 1.0 M aq KOH (5.0 mL) was then added and the resultant mixture was stirred at rt for 2 h before being extracted with Et_2O (2×10 mL). The combined organic extracts were washed with brine (10 mL) then dried and concentrated in vacuo to give **62** as a colourless oil (27 mg, 95%, >99:1 dr);[39c,d] $[\alpha]_D^{23}$ −35.8 (*c* 0.5 in EtOH); δ_H (400 MHz, $CDCl_3$) 1.13–1.37 (2H, m), 1.40–1.69 (3H, m), 1.74–1.87 (4H, m), 1.90–2.13 (3H, m) [C(1)*H*, C(2)H_2, C(3)H_A, C(5)H_A, C(6)H_2, C(7)H_2, C(8)H_2, C(8a)*H*], 3.05–3.40 (2H, m, C(3)H_B, C(5)H_B), 3.46 (1H, dd, *J* 10.2, 2.4, C(1′)H_A), 3.86 (1H, dd, *J* 10.2, 2.8, C(1′)H_B), 3.95 (1H, br s, O*H*); δ_C (100 MHz, $CDCl_3$) 24.1, 25.3, 25.4, 26.7 (*C*(2), *C*(6), *C*(7), *C*(8)), 41.0 (*C*(1)), 53.6, 53.9 (*C*(3), *C*(5)), 64.6 (*C*(1′)), 66.2 (*C*(8a)); *m/z* (ESI^+) 156 ($[M+H]^+$, 100%).

Method B: $LiAlH_4$ (1.0 M in THF, 4.20 mL, 4.20 mmol) was added to a stirred solution of **71** (140 mg, 0.71 mmol) in THF (5 mL) at 0 °C. The resultant mixture was heated at reflux for 48 h, then cooled to 0 °C. 1.0 M aq KOH (1 mL) was then added and the resultant mixture was stirred at rt for 2 h before being extracted with Et_2O (2×10 mL). The combined organic extracts were washed with brine (20 mL) then dried and concentrated in vacuo to give **62** as a colourless oil (110 mg, quant, >99:1 dr); $[\alpha]_D^{23}$ −35.8 (*c* 0.5 in EtOH).

4.2.32. Methyl (R,R)-3-oxooctahydroindolizine-1-carboxylate ***71****.*

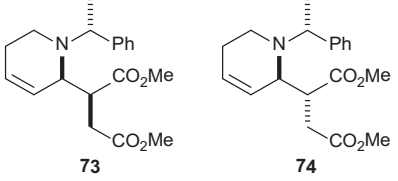


Step 1: BuLi (1.6 mL, 3.90 mmol) was added to a stirred solution of HTMP (0.67 mL, 3.90 mmol) in THF (10 mL) at −78 °C. After 30 min the reaction mixture was allowed to warm to rt and stirred at rt for a further 10 min, before being cooled back down to −78 °C. A solution of **49** (750 mg, 2.60 mmol) in THF (10 mL) at −78 °C was then added. The resultant mixture was stirred for 1 h at −78 °C then methyl bromoacetate (1.15 mL, 7.80 mmol) was added. The reaction mixture was then allowed to warm to rt over 16 h, satd aq NH_4Cl was added, and the resultant mixture was extracted with EtOAc (2×5 mL). The combined organic extracts were washed with brine (10 mL) then dried and concentrated in vacuo to give **69** in 90:10 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave *tert*-butyl (*R*,*R*)-2-[*N*(1′)-benzylpiperidin-2′-yl]-4-*tert*-butoxy-4-oxobutanoate **69** (90:10 dr) as a colourless oil (996 mg).

Step 2: A solution of **69** in 1.35 M HCl in MeOH (15 mL) was heated at 60 °C for 16 h. The reaction mixture was allowed to cool to rt and then concentrated in vacuo. The resulting residue was dissolved in CH_2Cl_2 (30 mL) and washed with satd aq $NaHCO_3$ (20 mL) and brine (20 mL), then dried and concentrated in vacuo to give methyl (*R*,*R*)-2-[N(1′)-benzylpiperidin-2′-yl]-4-methoxy-4-oxobutanoate **70** as a white solid (860 mg).

Step 3: $Pd(OH)_2/C$ (20% wt, 172 mg) was added to a solution of **70** (860 mg) in degassed MeOH (20 mL) and the resultant mixture was stirred under H_2 (1 atm) for 24 h. The reaction mixture was then filtered through Celite (eluent MeOH) and the filtrate was concentrated in vacuo. The residue was then dissolved in $CHCl_3$ (3 mL) and the resultant solution was heated at reflux for 16 h. The residue was dissolved in CH_2Cl_2 (30 mL) and washed with satd aq $NaHCO_3$ (30 mL) and brine (30 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 1:0; increased to neat EtOAc) gave **71** as a pale yellow oil (338 mg, 66% from **49**, >99:1 dr); $[\alpha]_D^{23}$ +20.3 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1730 (C=O), 1691 (C=O); δ_H (400 MHz, $CDCl_3$) 1.12–1.24 (1H, m), 1.35–1.85 (4H, m) [C(6)H_A, C(7)H_2, C(8)H_2] 1.90–1.95 (1H, m, C(6)H_B), 2.48–2.62 (1H, m, C(2)H_A), 2.64–2.66 (1H, m, C(5)H_A), 2.95–3.00 (1H, dd, *J* 9.5, 3.1, C(2)H_B), 3.35–3.51 (1H, m, C(1)*H*), 3.78–3.80 (1H, m, C(8a)*H*) 3.80 (3H, s, O*Me*), 4.15–4.20 (1H, m, C(5)H_B); δ_C (100 MHz, $CDCl_3$) 23.8, 24.2, 27.9 (*C*(6), *C*(7), *C*(8)), 32.5 (*C*(2)), 40.2 (*C*(1)), 40.7 (*C*(5)), 52.5 (O*Me*), 58.4 (*C*(8a)), 171.5, 171.8 (*C*(3), *C*O_2Me); *m/z* (ESI^+) 220 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{10}H_{15}NNaO_3^+$ ($[M+Na]^+$) requires 220.0944; found 220.0942.

4.2.33. Methyl (2S,2′R,αR)- and (R,R,R)-2-[N(1′)-(α-methylbenzyl)-1′,2′,5′,6′-tetrahydropyridin-2′-yl]-4-methoxy-4-oxobutanoate ***73*** *and* ***74****.*



NaHMDS (1.0 M in THF, 5.78 mL, 5.78 mmol) was added to a solution of **72**[8h] (1.00 g, 3.86 mmol) in THF (38 mL) at −78 °C and the resultant mixture was stirred at −78 °C for 30 min. Methyl bromoacetate (1.10 mL, 11.6 mmol) was then added, and the reaction mixture was allowed to warm to rt over 16 h before H_2O (10 mL) was added. The reaction mixture was then extracted with Et_2O (2×20 mL) and the combined organic extracts were sequentially washed with H_2O (20 mL) and brine (20 mL), then dried and concentrated in vacuo to give an 85:15 mixture of **73** and **74**. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 50:1) gave an 85:15 mixture of **73** and **74** as a colourless oil (942 mg, 74%).

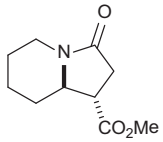
Data for mixture: ν_{max} (film) 3026, 2971, 2951 (C–H), 1732 (C=O); *m/z* (ESI^+) 354 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{19}H_{25}NNaO_4^+$ ($[M+Na]^+$) requires 354.1676; found 354.1675.

Data for **73**: δ_H (500 MHz, $CDCl_3$) 1.33 (3H, d, *J* 6.3, C(α)*Me*), 1.49–1.56 (1H, m, C(5′)H_A), 2.05–2.22 (1H, m, C(5′)H_B), 2.42–2.48 (1H, m, C(6′)H_A), 2.66–2.76 (1H, m, C(6′)H_B, C(3)H_A), 2.99 (1H, dd, *J* 16.7, 5.3, C(3)H_B), 3.07–3.13 (1H, m, C(2)*H*), 3.52–3.60 (1H, m, C(2′)

H), 3.70 (3H, s, O*Me*), 3.75 (3H, s, O*Me*), 3.79–3.84 (1H, m, C(α)*H*), 5.57–5.61 (1H, m, C(3′)*H*), 5.92–5.96 (1H, m, C(4′)*H*) 7.22–7.35 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 19.8 (*C*(5′)), 22.5 (C(α)*Me*), 35.5 (*C*(3)), 40.0 (*C*(6′)), 46.4 (*C*(2)), 51.7 (O*Me*), 51.9 (O*Me*), 55.1 (*C*(2′)), 58.0 (*C*(α)), 126.2 (*p-Ph*), 126.9, 128.1, 128.3 (*o*,*m-Ph*, *C*(3′), *C*(4′)), 145.5 (*i-Ph*), 172.7, 174.7 (*C*(1), *C*(4)).

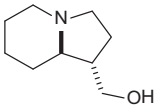
Data for **74**: δ_H (500 MHz, $CDCl_3$) [selected peaks] 5.65–5.70 (1H, m, C(3′)*H*), 5.85–5.89 (1H, m, C(4′)*H*).

4.2.34. Methyl (1S,8aR)-3-oxooctahydroindolizine-1-carboxylate **75**.



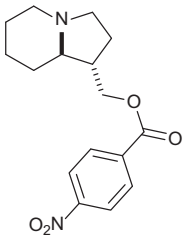
$Pd(OH)_2$/C (50% wt, 450 mg) was added to a solution of **73** (900 mg, 2.71 mmol, 85:15 dr) in degassed MeOH (20 mL) and the resultant mixture was stirred under H_2 (1 atm) for 16 h. The reaction mixture was then filtered through Celite (eluent MeOH) and the filtrate was concentrated in vacuo. The residue was then dissolved in CH_2Cl_2 (20 mL) and the resultant solution was washed with satd aq $NaHCO_3$ (20 mL) and brine (20 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 1:1; increased to neat EtOAc) gave **75** as a colourless oil (536 mg, 78%, >99:1 dr); $[\alpha]_D^{23}$ +13.7 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2941 (C–H), 1733 (C=O), 1685 (C=O); δ_H (400 MHz, $CDCl_3$) 1.10–1.43 (3H, m, C(6)H_A, C(7)H_A, C(8)H_A), 1.64–1.67 (1H, m, C(6)H_B), 1.83–1.89 (1H, m, C(7)H_B), 2.03–2.10 (1H, m, C(8)H_B), 2.52–2.62 (3H, m, C(2)H_2, C(5)H_A), 2.72–2.78 (1H, m, C(1)*H*), 3.46–3.51 (1H, m, C(8a)*H*), 3.78 (3H, s, O*Me*), 4.04–4.08 (1H, m, C(5)H_B); δ_C (100 MHz, $CDCl_3$) 23.4, 24.0 (*C*(6), *C*(7)), 32.5 (*C*(8)), 33.6 (*C*(2)), 40.0 (*C*(5)), 43.8 (*C*(1)), 52.3 (CO_2Me), 59.3 (*C*(8a)), 170.4, 171.8 (*C*(3), CO_2Me); *m*/*z* (ESI^+) 220 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{10}H_{15}NNaO_3^+$ ($[M+Na]^+$) requires 220.0944; found 220.0943.

4.2.35. (1S,8aR)-1-(Hydroxymethyl)octahydroindolizine **76**.



$LiAlH_4$ (1.0 M in THF, 4.20 mL, 4.20 mmol) was added to a stirred solution of **75** (140 mg, 0.71 mmol) in THF (5.0 mL) at 0 °C. The resultant mixture was heated at reflux for 3 days, then cooled to 0 °C. 1.0 M aq KOH (5.0 mL) was then added and the resultant solution was stirred at rt for 2 h before being extracted with Et_2O (4×10 mL). The combined organic extracts were washed with brine (10 mL), then dried and concentrated in vacuo to give **76** as a colourless oil (110 mg, quant, >99:1 dr);[39a,e] $[\alpha]_D^{23}$ +27.4 (*c* 1.0 in EtOH); ν_{max} (film) 3206, 2928, 2854, 1441; δ_H (400 MHz, $CDCl_3$) 1.10–1.32 (2H, m), 1.40–1.49 (1H, m), 1.50–1.65 (3H, m), 1.72–1.82 (1H, m), 1.84–2.08 (4H, m), 2.15–2.20 (1H, m) [C(1)*H*, C(2)H_2, C(3)H_A, C(5)H_A, C(6)H_2, C(7)H_2, C(8)H_2, C(8a)*H*], 2.26 (1H, br s, O*H*), 2.99–3.10 (2H, m, C(3)H_B, C(5)H_B), 3.56–3.65 (2H, m, C(1′)H_2); δ_H (400 MHz, CD_3CN) 1.14–1.26 (2H, m), 1.35–1.65 (4H, m), 1.71–1.89 (4H, m) [C(1)*H*, C(2)H_2, C(6)H_2, C(7)H_2, C(8)H_2, C(8a)*H*], 1.91–1.98 (1H, m), 2.05 (1H, app q, *J* 8.9), 2.86–2.92 (1H, m), 2.94–3.02 (1H, m) [C(3)H_2, C(5)H_2], 2.45 (1H, br s, O*H*), 3.41–3.51 (2H, m, C(1′)H_2);[48] δ_C (100 MHz, $CDCl_3$) 24.3, 25.2, 25.3, 30.5 (*C*(2), *C*(6), *C*(7), *C*(8)), 46.1 (*C*(1)), 53.4, 53.9 (*C*(3), *C*(5)), 64.9 (*C*(1′)), 67.3 (*C*(8a)); δ_C (100 MHz, CD_3CN) 24.7, 25.7, 25.8, 30.9 (*C*(2), *C*(6), *C*(7), *C*(8)), 46.7 (*C*(1)), 53.3, 53.6 (*C*(3), *C*(5)), 64.3 (*C*(1′)), 67.6 (*C*(8a));[48] *m*/*z* (ESI^+) 156 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_9H_{18}NO^+$ ($[M+H]^+$) requires 156.1383; found 156.1389.

4.2.36. (1S,8aR)-Octahydroindolizin-1-yl-methyl-4-nitrobenzoate **77**.



p-Nitrobenzoyl chloride (298 mg, 1.61 mmol) was added to a stirred solution of **76** (100 mg, 0.64 mmol) in CH_2Cl_2 (2 mL) and NEt_3 (2 mL) at rt, and the resultant solution was stirred for 20 h. The reaction mixture was then diluted with CH_2Cl_2 (20 mL) and the resultant solution was washed with satd aq $NaHCO_3$ (2×20 mL) then dried and concentrated in vacuo. Purification via flash column chromatography (eluent Et_2O) gave **77** as a yellow solid (89 mg, 46%, >99:1 dr); mp 50–52 °C; $[\alpha]_D^{23}$ +58.1 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2932 (C–H), 1722 (C=O); δ_H (400 MHz, $CDCl_3$) 1.15–1.35 (2H, m), 1.47–1.69 (4H, m), 1.77–1.80 (1H, m), 1.90–2.25 (5H, m), 3.03–3.08 (2H, m), 4.32–4.38 (2H, m, C(1′)H_2), 8.17 (2H, d, *J* 8.9, *Ar*), 8.27 (2H, d, *J* 8.9, *Ar*); δ_C (100 MHz, $CDCl_3$) 24.2, 25.2, 25.4, 30.5 (*C*(2), *C*(6), *C*(7), *C*(8)), 42.7 (*C*(8a)), 53.1, 53.4 (*C*(3), *C*(5)), 67.7 (*C*(1′)), 67.8 (*C*(1)), 123.6, 130.6, 135.6, 150.5 (*Ar*), 164.7 (*C*=O); *m*/*z* (ESI^+) 305 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{16}H_{21}N_2O_4^+$ ($[M+H]^+$) requires 305.1496; found 305.1499.

4.2.36.1. X-ray crystal structure determination for (1S,8aR)-**77**.

Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu Kα radiation using standard procedures at 150 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.[49]

X-ray crystal structure data for (1*S*,8a*R*)-**77** [$C_{16}H_{21}N_2O_{4.5}$]: *M*=626.71, triclinic, space group *P* 1, *a*=6.8943(2) Å, *b*=7.0698(3) Å, *c*=17.9334(6) Å, α=99.126(3)°, β=92.701(3)°, γ=114.185(3)°, *V*=781.17(5) Å^3, *Z*=2, μ=0.811 mm^{-1}, colourless plate, crystal dimensions=0.01×0.21×0.22 mm^3. A total of 29432 reflections were measured for 5<θ<27 and 29,432 reflections were used in the refinement. The final parameters were wR_2=0.098 and R_1=0.038 [$I>-3.0\sigma(I)$].

Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 834029. Copies of these data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif., or on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

Acknowledgements

The authors would like to thank New College, Oxford for a Junior Research Fellowship (A.D.S.), and Professors Stephen F. Martin and Ganesh Pandey, and Dr. Norbert Hoffmann for the efficient and useful exchange of data.

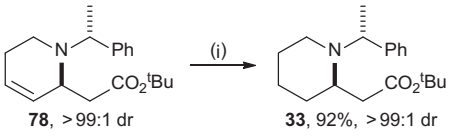
Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.09.038.

References and notes

1. (a) Fodor, G. B.; Colasanti, B. In *Alkaloids: Chemical and Biological Perspective*; Wiley: New York, NY, 1985; Vol. 3; p 1; (b) Christie, B. D.; Rapoport, H. *J. Org.*

Chem. **1985**, *50*, 1239; (c) Glorius, F.; Spielkamp, N.; Holle, S.; Goddard, R.; Lehmann, C. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 2850.
2. (a) Daly, J. W.; McNeal, E.; Gusovsky, F.; Ito, F.; Overman, L. E. *J. Med. Chem.* **1988**, *31*, 477; (b) Karpas, A.; Fleet, G. W. J.; Dwek, R. A.; Petursson, S.; Namgoong, S. K.; Ramsden, N. G.; Jacob, G. S.; Rademacher, T. W. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 9229; (c) Goss, P. E.; Baptiste, J.; Fernandes, B.; Baker, M.; Dennis, J. W. *Cancer Res.* **1994**, *54*, 1450; (d) Shin, J.; Seo, Y.; Cho, K. W.; Rho, J.-R.; Sim, C. J. *J. Nat. Prod.* **1997**, *60*, 611; (e) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645; (f) Saporito, R. A.; Garraffo, H. M.; Donnelly, M. A.; Edwards, A. L.; Longino, J. T.; Daly, J. W. *Proc. Natl. Acad. Sci. U.S. A.* **2004**, *101*, 8045.
3. Charette, A. B.; Grenon, M.; Lemire, A.; Pourashraf, M.; Martel, J. *J. Am. Chem. Soc.* **2001**, *123*, 11829.
4. (a) Taniguchi, T.; Ogasawara, K. *Org. Lett.* **2000**, *2*, 3193; (b) Schaudt, M.; Blechert, S. *J. Org. Chem.* **2003**, *68*, 2913.
5. (a) Hwang, Y. C.; Fowler, F. W. *J. Org. Chem.* **1985**, *50*, 2719; (b) Bailey, P. D.; Wilson, R. D.; Brown, G. R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1337; (c) Kobayashi, S.; Komiyama, S.; Ishitani, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 979; (d) Yao, S.; Johannsen, M.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **1998**, *37*, 3121; (e) Kobayashi, S.; Kusakabe, K.; Komiyama, S.; Ishitani, H. *J. Org. Chem.* **1999**, *64*, 4220; (f) Barluenga, J.; Aznar, F.; Ribas, C.; Valdés, C. *J. Org. Chem.* **1999**, *64*, 3736; (g) Buonora, P.; Olsen, J.-C.; Oh, T. *Tetrahedron* **2001**, *57*, 6099; (h) Avenoza, A.; Busto, J. H.; Cativiela, C.; Corzana, F.; Peregrina, J. M.; Zurbano, M. M. *J. Org. Chem.* **2002**, *67*, 598.
6. For instance, see: (a) Bailey, P. D.; Millwood, P. A.; Smith, P. D. *Chem. Commun.* **1998**, 633; (b) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781; (c) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953; (d) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701; (e) Kadouri-Puchot, C.; Comesse, S. *Amino Acids* **2005**, *29*, 101; (f) Källström, S.; Leino, R. *Bioorg. Med. Chem.* **2008**, *16*, 601.
7. (a) Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1991**, *2*, 183; (b) Davies, S. G.; Garrido, N. M.; Kruchinin, D.; Ichihara, O.; Kotchie, L. J.; Price, P. D.; Price Mortimer, A. J.; Russell, A. J.; Smith, A. D. *Tetrahedron: Asymmetry* **2006**, *17*, 1793; (c) Davies, S. G.; Nicholson, R. L.; Price, P. D.; Roberts, P. M.; Russell, A. J.; Savory, E. D.; Smith, A. D.; Thomson, J. E. *Tetrahedron: Asymmetry* **2009**, *20*, 758; (d) Davies, S. G.; Garner, A. C.; Nicholson, R. L.; Osborne, J.; Roberts, P. M.; Savory, E. D.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2009**, *7*, 2604; (e) Davies, S. G.; Mujtaba, N.; Roberts, P. M.; Smith, A. D.; Thomson, J. E. *Org. Lett.* **2009**, *11*, 1959; (f) Bentley, S. A.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Russell, A. J.; Thomson, J. E.; Toms, S. M. *Tetrahedron* **2010**, *66*, 4604; (g) Abraham, E.; Bailey, C. W.; Claridge, T. D. W.; Davies, S. G.; Ling, K. B.; Odell, B.; Rees, T. L.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Smith, L. J.; Storr, H. R.; Sweet, M. J.; Thompson, A. L.; Thomson, J. E.; Tranter, G. E.; Watkin, D. J. *Tetrahedron: Asymmetry* **2010**, *21*, 1797; (h) Abraham, E.; Claridge, T. D. W.; Davies, S. G.; Odell, B.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Smith, L. J.; Storr, H. R.; Sweet, M. J.; Thompson, A. L.; Thomson, J. E.; Tranter, G. E.; Watkin, D. J. *Tetrahedron: Asymmetry* **2011**, *22*, 69; (i) Brock, E. A.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Thomson, J. E. *Org. Lett.* **2011**, *13*, 1594; (j) Bagal, S. K.; Davies, S. G.; Fletcher, A. M.; Lee, J. A.; Roberts, P. M.; Scott, P. M.; Thomson, J. E. *Tetrahedron Lett.* **2011**, *52*, 2216.
8. For selected examples from this laboratory, see: (a) Davies, S. G.; Iwamoto, K.; Smethurst, C. A. P.; Smith, A. D.; Rodriguez-Solla, H. *Synlett* **2002**, 1146; (b) Davies, S. G.; Kelly, R. J.; Price Mortimer, A. J. *Chem. Commun.* **2003**, 2132; (c) Davies, S. G.; Burke, A. J.; Garner, A. C.; McCarthy, T. D.; Roberts, P. M.; Smith, A. D.; Rodriguez-Solla, H.; Vickers, R. J. *Org. Biomol. Chem.* **2004**, *2*, 1387; (d) Davies, S. G.; Haggitt, J. R.; Ichihara, O.; Kelly, R. J.; Leech, M. A.; Price Mortimer, A. J.; Roberts, P. M.; Smith, A. D. *Org. Biomol. Chem.* **2004**, *2*, 2630; (e) Abraham, E.; Candela-Lena, J. I.; Davies, S. G.; Georgiou, M.; Nicholson, R. L.; Roberts, P. M.; Russell, A. J.; Sánchez-Fernández, E. M.; Smith, A. D.; Thomson, J. E. *Tetrahedron: Asymmetry* **2007**, *18*, 2510; (f) Abraham, E.; Davies, S. G.; Millican, N. L.; Nicholson, R. L.; Roberts, P. M.; Smith, A. D. *Org. Biomol. Chem.* **2008**, *6*, 1655; (g) Abraham, E.; Brock, E. A.; Candela-Lena, J. I.; Davies, S. G.; Georgiou, M.; Nicholson, R. L.; Perkins, J. H.; Roberts, P. M.; Russell, A. J.; Sánchez-Fernández, E. M.; Scott, P. M.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2008**, *6*, 1665; (h) Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Smith, A. D. *Tetrahedron* **2009**, *65*, 10192; (i) Bentley, S. A.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Thomson, J. E. *Org. Lett.* **2011**, *13*, 2544; (j) Davies, S. G.; Ichihara, O.; Roberts, P. M.; Thomson, J. E. *Tetrahedron* **2011**, *67*, 216.
9. For selected examples from this laboratory, see: (a) Cailleau, T.; Cooke, J. W. B.; Davies, S. G.; Ling, K. B.; Naylor, A.; Nicholson, R. L.; Price, P. D.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2007**, *5*, 3922; (b) Davies, S. G.; Durbin, M. J.; Goddard, E. C.; Kelly, P. M.; Kurosawa, W.; Lee, J. A.; Nicholson, R. L.; Price, P. D.; Roberts, P. M.; Russell, A. J.; Scott, P. M.; Smith, A. D. *Org. Biomol. Chem.* **2009**, *7*, 761.
10. For selected examples from this laboratory, see: (a) Davies, S. G.; Garner, A. C.; Long, M. J. C.; Morrison, R. M.; Roberts, P. M.; Smith, A. D.; Sweet, M. J.; Withey, J. M. *Org. Biomol. Chem.* **2005**, *3*, 2762; (b) Aye, Y.; Davies, S. G.; Garner, A. C.; Roberts, P. M.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2008**, *6*, 2195; (c) Abraham, E.; Davies, S. G.; Docherty, A. J.; Ling, K. B.; Roberts, P. M.; Russell, A. J.; Thomson, J. E.; Toms, S. M. *Tetrahedron: Asymmetry* **2008**, *19*, 1356; (d) Davies, S. G.; Durbin, M. J.; Hartman, S. J. S.; Matsuno, A.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E.; Toms, S. M. *Tetrahedron: Asymmetry* **2008**, *19*, 2870.
11. Davies, S. G.; Smith, A. D.; Price, P. D. *Tetrahedron: Asymmetry* **2005**, *16*, 2833.
12. For similar approaches, see: (a) Enders, D.; Wiedemann, J. *Liebigs Ann.* **1997**, 699; (b) O'Brien, P.; Porter, D. W.; Smith, N. M. *Synlett* **2000**, 1336.
13. Davies, S. G.; Hughes, D. G.; Price, P. D.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E.; Williams, O. M. H. *Synlett* **2010**, 567.
14. Sengupta, S.; Mondal, S. *Tetrahedron* **2002**, *58*, 7983.
15. Hermet, J. R.; McGrath, M. J.; O'Brien, P.; Porter, D. W.; Gilday, J. *Chem. Commun.* **2004**, 1830.
16. Davies, S. G.; Costello, J. F.; Icihara, O. *Tetrahedron: Asymmetry* **1994**, *5*, 1999.
17. Davies, S. G.; Mulvaney, A. W.; Russell, A. J.; Smith, A. D. *Tetrahedron: Asymmetry* **2007**, *18*, 1554.
18. (a) Davies, S. G.; Nicholson, R. L.; Price, P. D.; Roberts, P. M.; Smith, A. D. *Synlett* **2004**, 901; (b) Davies, S. G.; Nicholson, R. L.; Price, P. D.; Roberts, P. M.; Savory, E. D.; Smith, A. D.; Thomson, J. E. *Tetrahedron: Asymmetry* **2009**, *20*, 756.
19. Bull, S. D.; Davies, S. G.; Fenton, G.; Mulvaney, A. W.; Prasad, P. S.; Smith, A. D. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3765.
20. The (3*S*,α*R*)-configuration within the major diastereoisomer **31** was assigned by comparison with literature data, see: Ref. 43.
21. The configurations within **33** and **34** were assigned by chemical correlation: hydrogenation of tetrahydropyridine **78** (>99:1 dr; see Ref. 8h) with Wilkinson's catalyst gave an authentic sample of piperidine **32** in 92% isolated yield and >99:1 dr.



78, >99:1 dr **33**, 92%, >99:1 dr

Reagents and conditions: (i) $Rh(PPh_3)_3Cl$ (5 mol %), H_2 (4 atm), EtOAc, rt, 12 h.

22. (a) Molander, G. A.; Harris, C. R. *J. Org. Chem.* **1997**, *62*, 7418; (b) Li, N.; Piccirilli, J. A. *J. Org. Chem.* **2004**, *69*, 4751.
23. Enantiopure (*R*)-α-methylbenzylamine (99% ee) is commercially available. Reductive alkylation of (*R*)-α-methylbenzylamine upon treatment with benzaldehyde and $NaBH_4$ gave (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine; subsequent deprotonation with BuLi in THF generated a pink solution of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **43**.
24. Holmes, A. B.; Smith, A. L.; Williams, S. F. *J. Org. Chem.* **1991**, *56*, 1393.
25. Davies, S. G.; Díez, D.; Dominguez, S. H.; Garrido, N. M.; Kruchinin, D.; Price, P. D.; Smith, A. D. *Org. Biomol. Chem.* **2005**, *3*, 1284.
26. Although the enantiomeric purity of **49** was not unambiguously determined, it was inferred as >99:1 er from the known diastereoisomic purities of the precurors **48**, **52** and **53** (>99:1 dr in each case), consistent with the known enantiopurity of the *N*-benzyl-*N*-(α-methylbenzyl)amine (>99:1 er) and *N*-benzyl-*N*-(*p*-methoxy-α-methylbenzyl)amine (>99:1 er) used.
27. We have recently published the sucessful application of this strategy in the synthesis of polysubstituted pyrrolizidines, see Ref. 7i.
28. Enantiopure (*R*)-*p*-methoxy-α-methylbenzylamine (99% ee) is commercially available. Reductive alkylation of (*R*)-*p*-methoxy-α-methylbenzylamine upon treatment with benzaldehyde and $NaBH_4$ gave (*R*)-*N*-benzyl-*N*-(*p*-methoxy-α-methylbenzyl)amine; subsequent deprotonation with BuLi in THF generated a yellow solution of lithium (*R*)-*N*-benzyl-*N*-(*p*-methoxy-α-methylbenzyl)amide **51**.
29. Coniine **1** is known to have potent neurotoxic effects, see: Rizzi, D.; Basile, C.; Dimaggio, A.; Sebastio, A.; Introna, F.; Rizzi, R.; Scatizzi, A.; Demarco, S.; Smialek, J. E. *Nephrol., Dial., Transplant.* **1991**, *6*, 939.
30. For other selected asymmetric syntheses of coniine **1**, see: (a) Al-awar, R. S.; Joseph, S. P.; Comins, D. L. *J. Org. Chem.* **1993**, *58*, 7732; (b) Enders, D.; Tiebes, J. *Liebigs Ann.* **1993**, 173; (c) Hattori, K.; Yamamoto, H. *Tetrahedron* **1993**, *49*, 1749; (d) Oppolzer, W.; Bochet, C. G.; Merrifield, E. *Tetrahedron Lett.* **1994**, *35*, 7015; (e) Hirai, Y.; Nagatsu, M. *Chem. Lett.* **1994**, 21; (f) Amat, M.; Llor, N.; Bosch, J. *Tetrahedron Lett.* **1994**, *35*, 2223; (g) Fréville, S.; Célérier, J. P.; Thuy, V. M.; Lhommet, G. *Tetrahedron: Asymmetry* **1995**, *6*, 2651; (h) Kim, Y. H.; Choi, J. Y. *Tetrahedron Lett.* **1996**, *37*, 5543; (i) Wilkinson, T. J.; Stehle, N. W.; Beak, P. *Org. Lett.* **2000**, 155; (j) Katritzky, A. R.; Qiu, G.; Yang, B.; Steel, P. J. *J. Org. Chem.* **1998**, *63*, 6699. See also Ref. 3.
31. For other selected asymmetric syntheses of coniceine **56**, see: (a) Takahata, H.; Kubota, M.; Takahashi, S.; Momose, T. *Tetrahedron: Asymmetry* **1996**, *7*, 3047; (b) Costa, A.; Najera, C.; Sansano, J. M. *Tetrahedron: Asymmetry* **2001**, *12*, 2205; (c) Park, S. H.; Kang, H. J.; Ko, S.; Park, S.; Chang, S. *Tetrahedron: Asymmetry* **2001**, *12*, 2621; (d) Hjelmgaard, T.; Gardette, D.; Tanner, D.; Aitken, D. J. *Tetrahedron: Asymmetry* **2007**, *18*, 671; (e) Castro, A.; Ramirez, J.; Juarez, J.; Teran, J. L.; Orea, L.; Galindo, A.; Gnecco, D. *Heterocycles* **2007**, *71*, 2699; (f) Lebrun, S.; Couture, A.; Deniau, E.; Grandclaudon, P. *Synthesis* **2008**, 2771; (g) Panchgalle, S. P.; Bidwai, H. B.; Chavan, S. P.; Kalkote, U. R. *Tetrahedron: Asymmetry* **2010**, *21*, 2399. See also Ref. 34.
32. β-Amino aldehydes are known to be unstable with respect to retro-Michael reactions, for example, see: Ref. 46.
33. Weymann, M.; Pfrengle, W.; Schollmeyer, D.; Kunz, H. *Synthesis* **1997**, 1151.
34. Munchof, M. J.; Meyers, A. I. *J. Org. Chem.* **1995**, *60*, 7084.
35. (a) Hirota, H.; Matsunaga, S.; Fusetani, N. *Tetrahedron Lett.* **1990**, *31*, 4163; (b) Whitlock, G. A.; Carreira, E. M. *J. Org. Chem.* **1997**, *62*, 7916; (c) Matsunaga, S.; Yamashita, T.; Tsukamoto, S.; Fusetani, N. *J. Nat. Prod.* **1999**, *62*, 1202; (d) Whitlock, G. A.; Carreira, E. M. *Helv. Chim. Acta* **2000**, *83*, 2007; (e) Yamazaki, N.; Dokoshi, W.; Kibayashi, C. *Org. Lett.* **2001**, *3*, 193; (f) Pilli, R. A.; Zanotto, P. R.; Böckelmann, M. A. *Tetrahedron Lett.* **2001**, *42*, 7003; (g) Ishii, K.; Sone, T.; Shigeyama, T.; Noji, M.; Sugiyama, S. *Tetrahedron* **2006**, *62*, 10865.
36. (a) Morley, C.; Knight, D. W.; Share, A. C. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2903; (b) Monterrey, I. M. G.; González-Muñiz, R.; Herranz, R.; Garcia-López, M. T. *Tetrahedron* **1995**, *51*, 2729.

37. Within this area, Monterrey et al. have shown that alkylation of *N*-Cbz protected piperidin-2-ylacetates with ethyl bromoacetate can lead to successful ring closure by removal of the *N*-Cbz protecting group in a tandem hydrogenolysis/hydrogenation step to give the corresponding hexahydroindolizin-3-one, see: Ref. 36b.
38. It was noted that cyclisation of **67** to give **68** occurred while the crude product mixture was allowed to stand in solution in $CDCl_3$.
39. (a) Nagao, Y.; Dai, W.; Ochiai, M.; Tsukagoshi, S.; Fujita, E. *J. Org. Chem.* **1990**, *55*, 1148; (b) Pandey, G.; Lakshmaieh, G. *Tetrahedron Lett.* **1993**, *34*, 4861; (c) Pandey, G.; Reddy, G. D.; Chakrabarti, D. *J. Chem. Soc., Perkin Trans. 1* **1996**, 219; (d) Bertrand, S.; Hoffmann, N.; Pete, J.-P. *Eur. J. Org. Chem.* **2000**, 2227; (e) Amorde, S. M.; Jewett, I. T.; Martin, S. F. *Tetrahedron* **2009**, *65*, 3222; (f) Nagao, Y.; Dai, W.-M.; Ochiai, M.; Tsukagoshi, S.; Fujita, E. *J. Am. Chem. Soc.* **1988**, *110*, 289; (g) Bertrand, S.; Hoffmann, N.; Pete, J.-P. *Tetrahedron Lett.* **1999**, *40*, 3173.
40. Heating a solution of **75** in MeOH at 60 °C in the presence of NaOMe for 3 days gave returned starting material only.
41. Baenzinger, M.; Gobbi, L.; Riss, B. P.; Schaefer, F.; Vaupel, A. *Tetrahedron: Asymmetry* **2000**, *11*, 2231.
42. Yasuhara, T.; Nishimura, K.; Yamashita, M.; Fukuyama, N.; Yamada, K.; Muraoka, O.; Tomioka, K. *Org. Lett.* **2003**, *5*, 1123.
43. Chippindale, A. M.; Davies, S. G.; Iwamoto, K.; Parkin, R. M.; Smethurst, C. A. P.; Smith, A. D.; Rodriguez-Solla, H. *Tetrahedron* **2003**, *59*, 3253.
44. Stille, J. R.; Grubbs, R. H. *J. Org. Chem.* **1987**, *54*, 434.
45. Davies, S. G.; Ichihara, O.; Lenoir, I.; Walters, I. A. S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1411.
46. Carruthers, W.; Moses, R. C. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2251.
47. Carruthers, W.; Coggins, P.; Weston, J. B. *J. Chem. Soc., Chem. Commun.* **1991**, 117.
48. Our NMR spectroscopic data for **76** in CD_3CN were in excellent agreement with those kindly provided by Professor Stephen F. Martin, see also Ref. 39e.
49. Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.