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Ring-closing iodoamination of homoallylic amines for the synthesis of polysubstituted pyrrolidines: application to the asymmetric synthesis of (−)-codonopsinine

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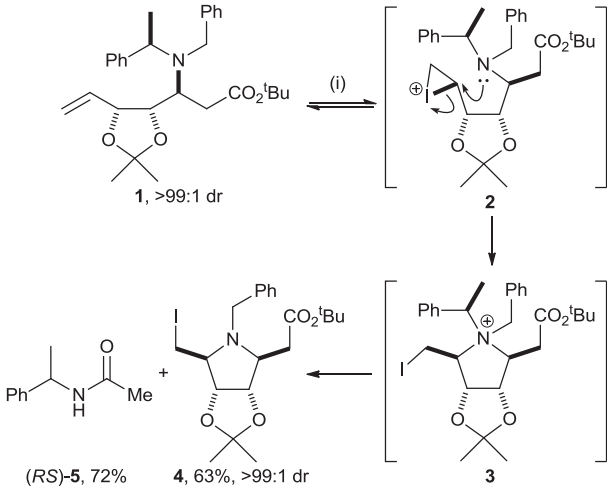
ABSTRACT

Ring-closing iodoamination of (*E*)-configured, *N*-α-methyl-*p*-methoxybenzyl protected homoallylic amines upon treatment with I_2 and $NaHCO_3$ in MeCN occurs with concomitant loss of the *N*-α-methyl-*p*-methoxybenzyl group to give 3-iodopyrrolidines in >99:1 dr. This transformation was used as one of the key steps in the total asymmetric synthesis of (−)-codonopsinine, which was achieved in seven steps (from commercially available *tert*-butyl crotonate) in 5% overall yield and >99:1 dr.

1. Introduction

We have recently reported a ring-closing iodoamination protocol (which proceeds with concomitant N-debenzylation) as the key step in the total asymmetric syntheses of piperidine,[1] pyrrolidine[2] and pyrrolizidine[3] scaffolds. For example, iodoamination of **1** 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 diastereospecific cyclisation to give quaternary ammonium ion **3** that undergoes preferential loss of the *N*-α-methylbenzyl cation, which is then trapped by MeCN in a Ritter reaction to give racemic *N*-α-methylbenzylacetamide (*RS*)-**5** in 72% yield, in addition to pyrrolidine **4**, which was isolated in 63% yield and >99:1 dr (Scheme 1).

During the course of these studies we observed that the nature of the *N*-protecting groups had a dramatic effect on the reaction outcome. For example, when *N*-α-methyl-*p*-methoxybenzyl substituted amine **7** was treated with $AgBF_4$ in MeCN, piperidine **8** was formed in far greater yield than when the corresponding *N*-α-methylbenzyl substituted amine **6** was reacted under identical conditions.[1] Furthermore, transannular iodoamination of *N*-α-methyl-*p*-methoxybenzyl substituted **10** gave pyrrolizidine **11** [an intermediate in our synthesis of (−)-7a-*epi*-hyacinthacine A_1 **13**], whereas reaction of the corresponding *N*-α-methylbenzyl



Scheme 1. Reagents and conditions: (i) I_2, $NaHCO_3$, MeCN, rt, 20 h.

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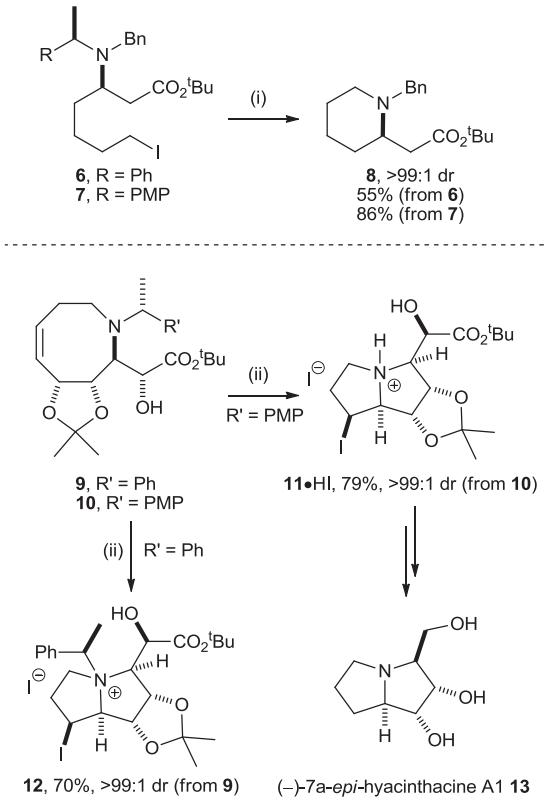
substituted analogue **9** under identical conditions gave only ammonium **12**, which could not be *N*-deprotected (Scheme 2).[3]



Scheme 2. Reagents and conditions: (i) $AgBF_4$, MeCN, 80 °C, 16 h; (ii) I_2, $NaHCO_3$, CH_2Cl_2 (EtOH stabilised), rt, 12 h [PMP=*p*-methoxyphenyl].

We envisaged that this ring-closing iodoamination strategy would also be applicable to the synthesis of pyrrolidine alkaloids and selected (−)-codonopsinine **14** (Fig. 1) as a target to probe the scope of this methodology. (−)-Codonopsinine **14** was isolated in 1969 from *Codonopsis clematidea*, a flowering plant native to East Asia.[4] Its structure was unambiguously assigned in 1986 by Kibayashi and co-workers via single crystal X-ray diffraction analysis of an intermediate in their total synthesis of (+)-codonopsinine **14**.[5] Several syntheses of codonopsinine **14** have been reported. Most of these approaches are enantiospecific, starting from either L-xylose,[6–8] D-alanine,[9,10] L-threonine,[11] D-tartaric acid,[12] L-tartaric acid,[13] L-pyroglutamic acid[14,15] or D-ribose.[16] In addition, one total racemic synthesis[17] and one total asymmetric synthesis[18] of codonopsinine **14** are also known. A range of diverse synthetic strategies have been adopted in these syntheses, including the diastereoselective addition of Grignard reagents to cyclic nitrones, the decarboxylative cyclisation of allylic carbamates, the Heck reaction of endocyclic enecarbamates and intramolecular S_N2-type displacement reactions, amongst other approaches.

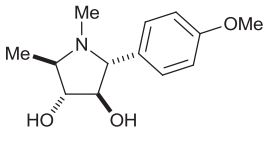


Fig. 1. The structure of (−)-codonopsinine **14**.

By analogy to our previous results, our strategy for the synthesis of (−)-codonopsinine **14** involved treatment of a homoallylic amine **17** with I_2 leading to reversible formation of iodonium species **18**, which may undergo diastereospecific cyclisation to form ammonium ion **19**, with the electron donating *p*-methoxyphenyl group being expected to stabilise the transition state during the ring-closing iodoamination step. Subsequent in situ loss of one of the nitrogen protecting groups would then give the corresponding 3-iodopyrrolidine **20**. We therefore set out to screen a range of substrates, incorporating *p*-methoxy groups on the different aryl rings of the *N*-benzyl protecting groups (i.e., R^1 and R^2) so that the structural/electronic requirements of the aforementioned N-debenzylation step could be probed further. It was envisaged that the C(2)-*p*-methoxyphenyl group within **20** could then be exploited in the manipulation of the C(3)-iodide functionality: neighbouring group participation of the C(2)-*p*-methoxyphenyl group followed by regioselective ring-opening of phenonium ion intermediate **21** was expected to install oxygen functionality at C(3) with the correct configuration for (−)-codonopsinine **14**. It was envisaged that homoallylic amine **17** could be easily synthesised from *tert*-butyl crotonate **15** using our asymmetric aminohydroxylation protocol,[19,20] whereby conjugate addition of enantiopure lithium amides to **15**, followed by in situ oxidation of the intermediate lithium (*Z*)-β-amino enolate with (−)-camphorsulfonyloxaziridine [(−)-CSO],[21] gives *anti*-α-hydroxy-β-amino esters **16** with high diastereoselectivity. Subsequent protection of the hydroxyl group within **16**, reduction of the *tert*-butyl ester moiety and Wittig olefination of the resultant aldehyde should then give access to a range of homoallylic amines **17** (Fig. 2). Part of this work has been communicated previously.[22]

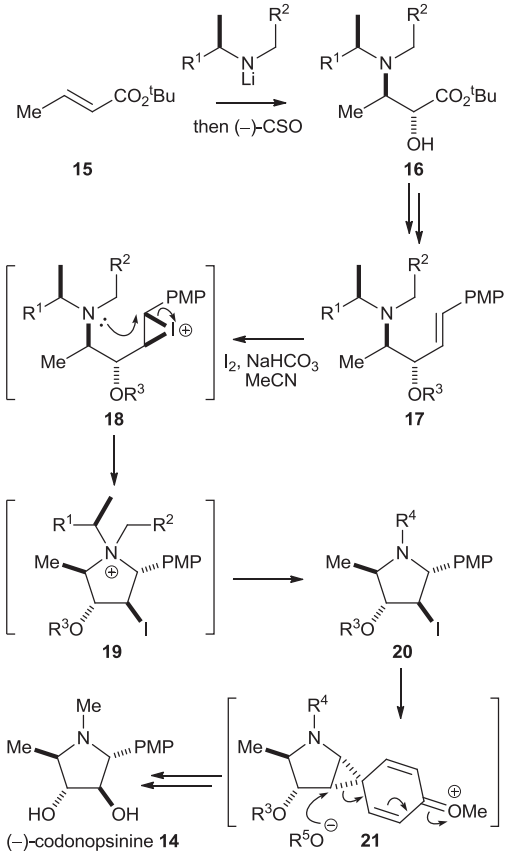


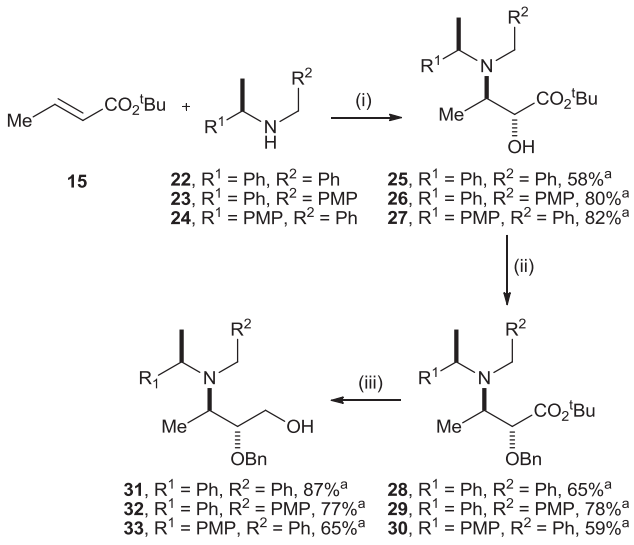
Fig. 2. Proposed synthetic strategy towards (−)-codonopsinine **14** [PMP=*p*-methoxyphenyl].

2. Results and discussion

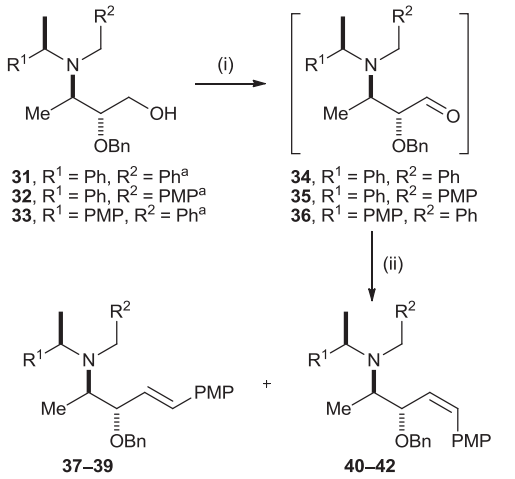
2.1. Development of a ring-closing iodoamination protocol

The conjugate addition of the lithium amides derived from **22**, **23** and **24** to *tert*-butyl crotonate **15**, followed by in situ oxidation of the intermediate lithium (*Z*)-β-amino enolates with (−)-CSO,[21] gave α-hydroxy-β-amino esters **25**, **26** and **27** in 58, 80 and 82% isolated yield, respectively, as single diastereoisomers (>99:1 dr) in each case (Scheme 3). The relative configurations within **25** and **27** were unambiguously established by single crystal X-ray diffraction analyses,[23] with the absolute (*R*,*R*,*R*)-configurations within **25** and **27** assigned relative to the known configurations of the (*R*)-α-methylbenzyl fragments (Fig. 3); the configuration within **26** was therefore confidently assigned by analogy. This stereochemical outcome is entirely consistent with the well-established diastereofacial selectivity observed upon tandem conjugate addition of a secondary lithium amide derived from α-methylbenzylamine and in situ enolate oxidation with (−)-CSO.[19,20] Subsequent protection of the C(2)-hydroxyl groups within β-amino esters **25**–**27** as the corresponding *O*-benzyl ethers was achieved upon treatment with NaH and BnBr, giving **28**–**30** in 59–78% yield, and reduction of esters **28**–**30** upon treatment with $LiAlH_4$ gave the corresponding alcohols **31**–**33** in 65–87% yield (Scheme 3).

Oxidation of alcohols **31**–**33** under Swern conditions, followed by Wittig olefination of the resultant aldehydes with the ylid derived from 4-methoxybenzyl triphenylphosphonium chloride produced ~2:1 mixtures of diastereoisomeric olefins, with the (*E*)-isomers **37**–**39** as the major products in each case. After purification of the crude reaction mixtures, **37**, **39**, **40** and **42** were all isolated as single diastereoisomers (>99:1 dr) in reasonable yield, although mixed fractions were also isolated, whilst **38** and **41** proved to be inseparable by chromatography and were therefore isolated as a 66:34 mixture in 71% combined yield (Scheme 4). The configurations within **37**–**42** were initially assigned from the diagnostic values of the ^{1}H NMR ^3J olefinic coupling constants: for the (*E*)-diastereoisomers **37**–**39**, values of 15.8–16.1 Hz were observed, whereas the (*Z*)-diastereoisomers **40**–**42** all displayed ^3J olefinic coupling constants of 12.0 Hz. The relative configuration within **42** was also unambiguously confirmed by single crystal X-ray diffraction analysis;[23] this analysis also allowed the



Scheme 3. Reagents and conditions: (i) BuLi, THF, −78 °C, 2.5 h, then (−)-CSO, −78 °C to rt, 12 h; (ii) NaH, THF, 0 °C, 1 h, then BnBr, rt, 12 h; (iii) $LiAlH_4$, THF, 0 °C, 30 min, then rt, 16 h [[a]>99:1 dr; PMP=*p*-methoxyphenyl].



R¹	R²	products	dr [(*E*):(*Z*)]	products isolated (yield over 2 steps)
Ph	Ph	(*E*)-**37**, (*Z*)-**40**	67:33	**37** (25%[a]), **40** (15%[a])
Ph	PMP	(*E*)-**38**, (*Z*)-**41**	66:34	**38**:**41** (71%,[b] 66:34 dr)
PMP	Ph	(*E*)-**39**, (*Z*)-**42**	65:35	**39** (28%[a]), **42** (15%[a])

Scheme 4. Reagents and conditions: (i) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, 30 min, then Et_3N, −78 °C to rt, 1 h; (ii) BuLi, $[4\text{-}MeOC_6H_4CH_2PPh_3]^+$ $[Cl]^-$, THF, −78 °C, 30 min, then rt, 12 h [[a]>99:1 dr; [b]combined yield; PMP=*p*-methoxyphenyl].

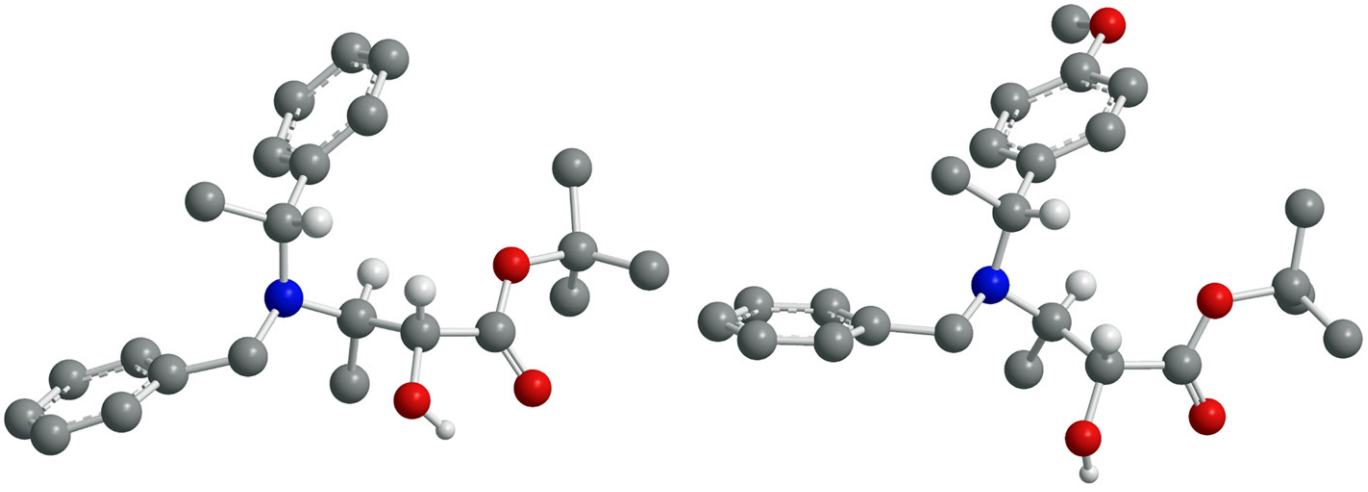


Fig. 3. X-ray crystal structures of **25** [left] and **27** [right] (selected H atoms are omitted for clarity).

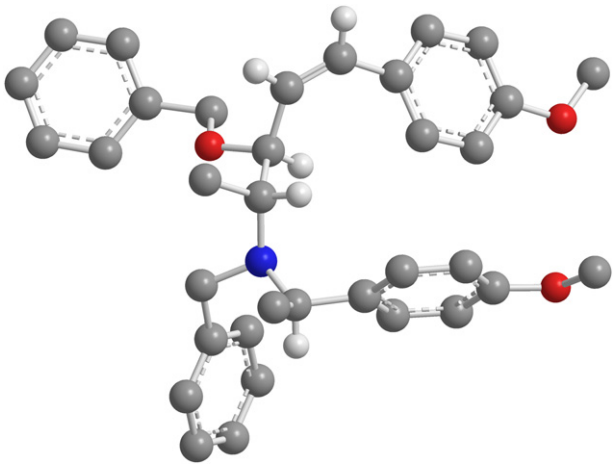
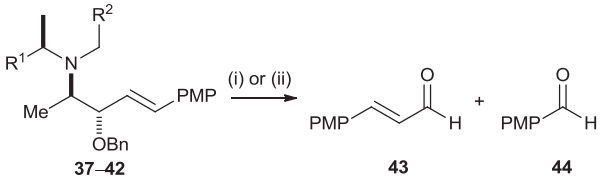


Fig. 4. X-ray crystal structure of **42** (selected H atoms are omitted for clarity).

(3*S*,4*R*,α*R*,*Z*)-absolute configuration within **42** to be unambiguously assigned relative to the known configuration of the (*R*)-α-methyl-*p*-methoxybenzyl fragment (Fig. 4).

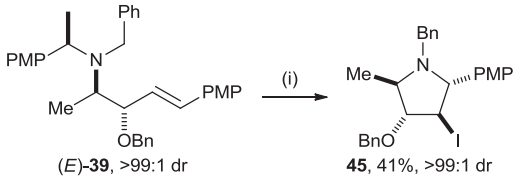
Ring-closing iodoamination of **37**–**42** was attempted using our previously developed conditions, viz treatment with I_2 and $NaHCO_3$ in either MeCN[2] or CH_2Cl_2.[3] A complex mixture of unidentifiable products was formed in each case upon reaction of either (*E*)-**37**, (*Z*)-**40**, the 66:34 mixture of (*E*)-**38** and (*Z*)-**41**, or (Z)-**42** according to the procedure involving CH_2Cl_2. The analogous reactions using MeCN as the solvent gave incomplete conversion to α,β-unsaturated aldehyde **43** and *p*-anisaldehyde **44** by analysis of the ^{1}H NMR spectra of the crude reaction mixtures. Presumably, **43** and **44** are formed as a result of a single electron oxidation process followed by fragmentation. Upon reaction of (*E*)-**39** with I_2 according to the protocol using CH_2Cl_2 as the solvent a complex mixture of unidentifiable products was again formed (Scheme 5). However, upon treatment of (*E*)-**39** (>99:1 dr) with I_2 and $NaHCO_3$ in MeCN the ring-closing iodoamination reaction proceeded to give 3-iodopyrrolidine **45** in 90% conversion and >99:1 dr. Purification of the crude reaction mixture enabled isolation of **45** in 41% yield and >99:1 dr (Scheme 6). Single crystal X-ray diffraction analysis of the corresponding hydrochloride salt **45**·HCl allowed the relative configuration within **45** to be unambiguously assigned.[23] The absolute (*R*,*R*,*R*,*R*)-configuration within **45** was initially assigned relative to the known configurations of the C(4)- and C(5)-stereocentres. Furthermore, the determination of a Flack *x* parameter[24,25] of



37–42 **43** **44**

substrate	R^1	R^2	dr [(*E*):(*Z*)]	cond.	prodict distribution
(*E*)-**37**/(*Z*)-**40**	Ph	Ph	100:0	(i)	complex mixture
			0:100	(i)	complex mixture
			100:0	(ii)	45:55 [**37**:**43**]
			67:33	(ii)	38:37:25 [**37**:**40**:**43**]
(*E*)-**38**/(*Z*)-**41**	Ph	PMP	66:34	(i)	complex mixture
			66:34	(ii)	10:30:50 [**41**:**43**:**44**]
(*E*)-**39**/(*Z*)-**42**	PMP	Ph	100:0	(i)	complex mixture
			0:100	(i)	complex mixture
			0:100	(ii)	60:40 [**42**:**43**]

Scheme 5. Reagents and conditions: (i) $NaHCO_3$, I_2, CH_2Cl_2, rt, 12 h; (ii) $NaHCO_3$, I_2, MeCN, −20 °C, 2 h, then rt, 20 h [PMP=*p*-methoxyphenyl].



(*E*)-**39**, >99:1 dr **45**, 41%, >99:1 dr

Scheme 6. Reagents and conditions: (i) $NaHCO_3$, I_2, MeCN, −20 °C, 2 h, then rt, 20 h [PMP=*p*-methoxyphenyl].

−0.039(8) for the crystal structure of **45**·HCl allowed the absolute (*R*,*R*,*R*,*R*)-configuration within **45** to be confirmed unambiguously (Fig. 5). Extensive optimisation studies of this ring-closing iodoamination reaction were conducted, altering the reaction time and temperature along with increasing the number of equivalents of I_2 and $NaHCO_3$, although this did not improve the yield of **45** obtained.

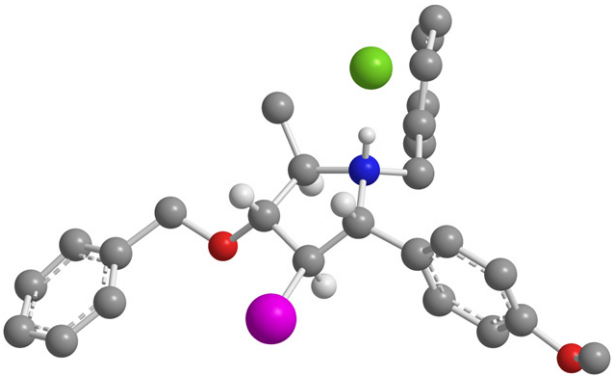


Fig. 5. X-ray crystal structure of **45**·HCl (selected H atoms are omitted for clarity).

As hypothesised, the nature of the nitrogen protecting groups was found to have a dramatic effect on the reactivity of the homoallylic amine substrates **37**–**42**, although the olefin geometry was also found to be important: the *N*-α-methyl-*p*-methoxybenzyl substrate (*E*)-**39** successfully produced 3-iodopyrrolidine **45** in 90% conversion, whereas the *N*-α-methylbenzyl substrates **37**, **38**, **40** and **41**, and also (*Z*)-**42** gave only returned starting material or degradation products. In the former case, the formation of **45** as a single diastereoisomer in the ring-closing iodoamination step suggests that cyclisation occurs via the attack of an iodonium species (which is presumably formed reversibly from **39**), as cyclisation via the corresponding carbonium ion at C(1) would be expected to give rise to a mixture of diastereoisomeric pyrrolidines. The diastereoselectivity of the ring-closing iodoamination step can then be rationalised by considering the intermediate iodonium species **46** and **49**. Within transition state **50** for the cyclisation of iodonium **49**, both the C(3)-benzyloxy and C(4)-methyl groups occupy pseudo-axial positions and experience unfavourable steric interactions with the nitrogen protecting groups (i.e., R^1 and R^2, one of which is α-branched). For cyclisation of iodonium **46**, the C(3)-benzyloxy and C(4)-methyl groups occupy pseudo-equatorial positions and do not suffer unfavourable steric interactions with the nitrogen protecting groups in transition state **47**. In fact, the *N*-benzyl or *N*-α-methyl-*p*-methoxybenzyl group at R^2 within transition state **47** can minimise 1,2-strain with the C(1)-*p*-methoxyphenyl substituent by adopting a conformation with the aryl group away from the site of reaction; this is not possible within the disfavoured transition state **50** as, regardless of the conformation of the R^2 group, unfavourable steric interactions will be encountered between R^2 and either the C(1)-*p*-methoxyphenyl or C(4)-methyl groups (Fig. 6). It is noteworthy that the corresponding (*Z*)-configured substrate **42** did not undergo selective ring-closing iodoamination, rather it gave returned starting material and produced degradation product **43**. It is observed in the crystal structure

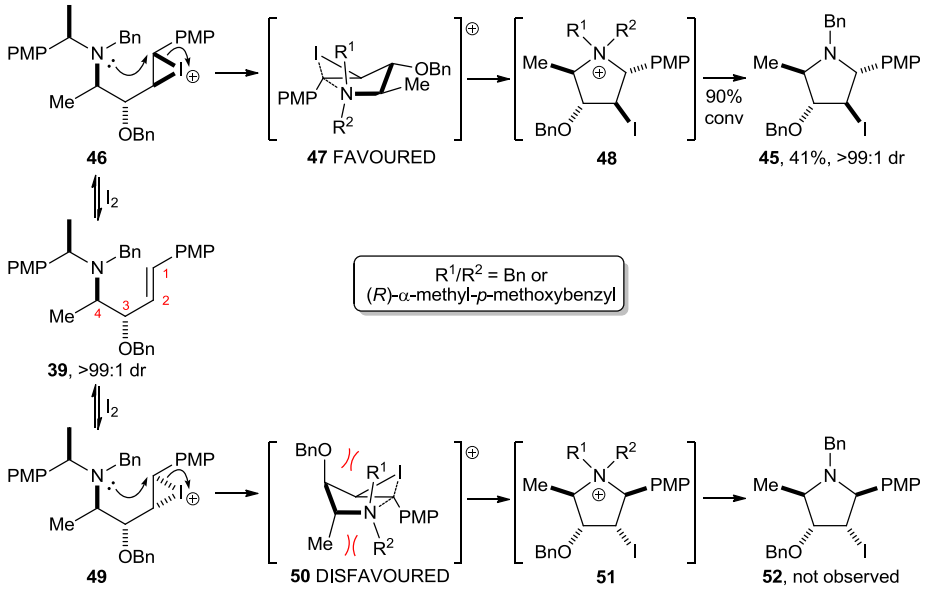
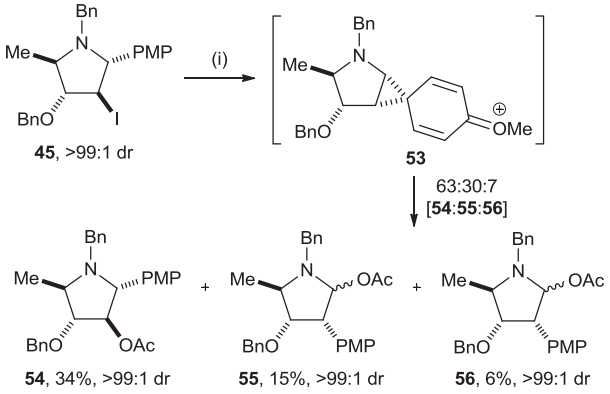


Fig. 6. The origin of diastereoselectivity in the ring-closing iodoamination reaction [PMP=*p*-methoxyphenyl].

of **42** that the C(2′)–C(1′)–C(1)–C(2) dihedral angle is 42.1° and therefore the extent of conjugation between the *p*-methoxyphenyl ring and the olefin will be significantly reduced compared to the idealised coplanar structure. Two potential rationales for the differing reactivities of (*E*)-**39** and (*Z*)-**42** can therefore be proposed: firstly, in (*Z*)-**42**, the alkene is less nucleophilic and so reacts with I_2 at a slower rate, allowing degradation pathways to compete with iodoamination. This is in contrast with (*E*)-**39**, where it is assumed that the same dihedral angle is closer to 0° to maximise conjugation, thus making the double bond more electron-rich and nucleophilic. Alternatively, adverse steric effects may dictate that iodonium intermediates formed from (*Z*)-**42** are unstable and so decompose to give degradation product **43**.

2.2. The asymmetric synthesis of (−)-codonopsinine

As (−)-codonopsinine **14** possesses the same 'all-*trans*' configuration as 3-iodopyrrolidine **45**, elaboration of **45** to enable the total synthesis of (−)-codonopsinine **14** required substitution of the iodide substituent at C(3) with retention of configuration. A double inversion strategy [e.g., S_N2 displacement with acetate, hydrolysis of the resultant C(3)-acetoxy substituted pyrrolidine then Mitsunobu reaction] was considered, but a strategy reliant on neighbouring group participation by the C(2)-*p*-methoxyphenyl group (i.e., a stereoselective S_N1-type process) was envisaged to be more efficient in installing the oxygen functionality at C(3) with the correct configuration, with subsequent deprotection then providing access to (−)-codonopsinine **14**. In order to promote an S_N1-type reaction, **45** was treated with AgOAc in AcOH. Under these reaction conditions, a 63:30:7 mixture of **54** and two different regioisomers, **55** and **56**, was produced. Upon purification of this mixture, the major product **54** was isolated in 34% yield as a single diastereoisomer, and the regioisomeric pyrrolidines **55** and **56** were also isolated in 15 and 6% yield, respectively, and >99:1 dr in each case (Scheme 7). The relative configuration within **54** was determined by ^{1}H NMR NOE spectroscopic analysis. The atom connectivity within the regioisomeric products **55** and **56** was established by a combination of ^{1}H NMR COSY, and ^{1}H and ^{13}C NMR HSQC and HMBC analyses. Crucially, in both cases the peaks corresponding to the C(2)*H* protons were found at significantly higher chemical shifts [δ_H=5.79 ppm for C(2)*H* within **55** and δ_H=5.68 ppm for C(2)*H* within **56**] relative to the corresponding

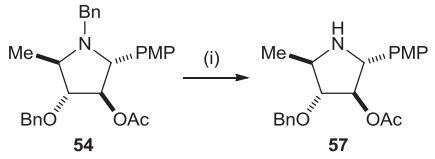


Scheme 7. Reagents and conditions: (i) AgOAc, AcOH, 30 °C, 12 h [PMP=*p*-methoxyphenyl].

C(3)-acetoxy analogue [δ_H=5.23 ppm for C(3)*H* within **54**]. Unfortunately, ^{1}H NMR NOE spectroscopic analyses of **55** and **56** were not conclusive and therefore their relative configurations could not be confidently assigned. The appearance of regioisomers **55** and **56** in the product distribution lends support to the original hypothesis that a mechanism involving neighbouring group participation via phenonium ion intermediate **53** was occurring, and giving rise to retention of configuration upon attack of the acetate anion at C(3) within **53**. Interestingly, resubjection of **55** to the reaction conditions for a further 12 h produced an 81:19 mixture of **55** and **56**, respectively, although **54** was not observed in this case.

With **54** in hand, deprotection towards (−)-codonopsinine **14** was commenced. The deprotection strategy involved removing the *N*- and *O*-benzyl groups upon hydrogenolysis before transesterification and N-methylation (under literature conditions)[28] to afford (−)-codonopsinine **14**. Upon hydrogenolysis of **54**, in the presence of Pd/C under an atmosphere of H_2, N-debenzylation was found to occur readily to give **57**, although O-debenzylation was not observed (Scheme 8). As a result, **57** was resubjected to the reaction conditions but this afforded a complex mixture. A range of conditions were subsequently screened in an attempt to remove the *O*-benzyl protecting group within **57**, but without success.

It was therefore decided that selection of an alternative *O*-protecting group at the start of the synthesis would be a suitable solution to this O-debenzylation problem. Protection of the C(2)-hydroxyl group within **27** as the *O*-MOM ether was anticipated to



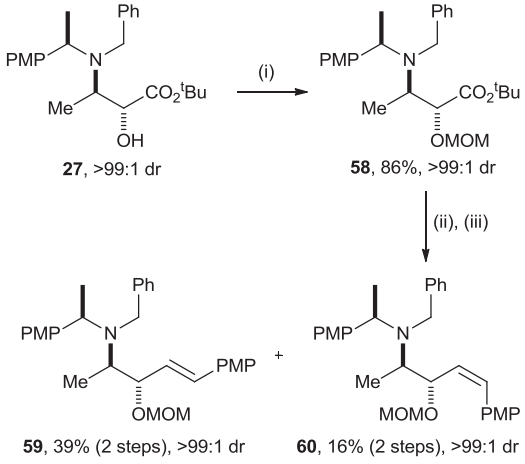
Scheme 8. Reagents and conditions: (i) Pd/C, MeOH, H_2 (1 atm), rt, 24 h [PMP=*p*-methoxyphenyl].

be a suitable alternative to the *O*-benzyl group strategy used previously. Thus, *O*-MOM protection of **27** was achieved using MOMCl and NaH in DMF giving **58** in 86% yield and >99:1 dr after chromatographic purification. It was then found that reduction of β-amino ester **58** to the corresponding aldehyde could be achieved directly upon treatment with DIBAL-H at −78 °C. Subsequent Wittig olefination using the same conditions as for the analogous *O*-benzyl substituted aldehydes **34**–**36** afforded a ~2:1 mixture of *O*-MOM protected olefins (*E*)-**59** and (*Z*)-**60**, which were isolated in 39 and 16% yield over two steps, respectively, and in >99:1 dr in each case; a 50:50 mixture of **59** and **60** was also isolated in 13% combined yield after purification (Scheme 9). In each case, the configurations of the newly formed double bonds within **59** and **60** were assigned by ^{1}H NMR ^3J coupling constant analyses, with diagnostic olefinic coupling constants being observed [$J_{1,2}$=15.9 Hz for (*E*)-**59**; $J_{1,2}$=11.9 Hz for (*Z*)-**60**].

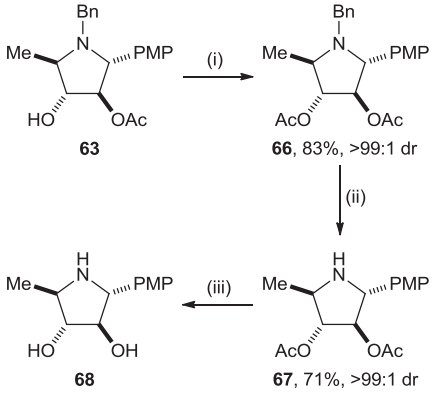
With enantiopure homoallylic amine (*E*)-**59** in hand, ring-closing iodoamination of **59** upon treatment with $NaHCO_3$ and I_2 in MeCN gave 3-iodopyrrolidine **61** as the major product. As **61** could not be separated from an unidentified impurity, this mixture was immediately subjected to AgOAc in AcOH, giving **62** as a single diastereoisomer (>99:1 dr) in 37% isolated yield (from **59**). The relative configurations within both **61** and **62** were determined by ^{1}H NMR NOE spectroscopic analyses. Removal of the *O*-MOM protecting group from within **62** was achieved upon treatment with methanolic HCl to give **63**, which was immediately reacted with K_2CO_3 in MeOH to effect transesterification to the corresponding diol **64**. Unfortunately, attempted elaboration of **64** directly to (−)-codonopsinine **14** via an N-debenzylation/reductive methylation protocol was not successful, and instead cleavage of the N(1)–C(2) bond within **64** was observed instead to give ring-opened *N*,*N*-dimethylamine **65** as the major product (Scheme 10).

It was envisaged that N-debenzylation of diacetoxy species **66** would have a greater chance of proceeding without ring-opening, since N-debenzylation of bis-*O*-protected **54** had previously occurred without reductive cleavage of the N(1)–C(2) bond. Therefore, the C(4)-hydroxyl group within **63** was *O*-acetyl protected upon treatment with Ac_2O and pyridine to give **66** in 83% isolated yield and >99:1 dr. Subsequent hydrogenolysis of **66** in the presence of $Pd(OH)_2$/C gave quantitative conversion to *N*-debenzylated pyrrolidine **67**, which was isolated in 71% yield. Transesterification of **67** gave a small sample of diol **68**, which was found to be difficult to purify and isolate. Unfortunately, attempted N-methylation of **68** upon treatment of the product mixture with MeI, using the conditions kindly supplied by Reissig and Chowdhury[17] gave a complex mixture from which (−)-codonopsinine **14** could not be isolated (Scheme 11).

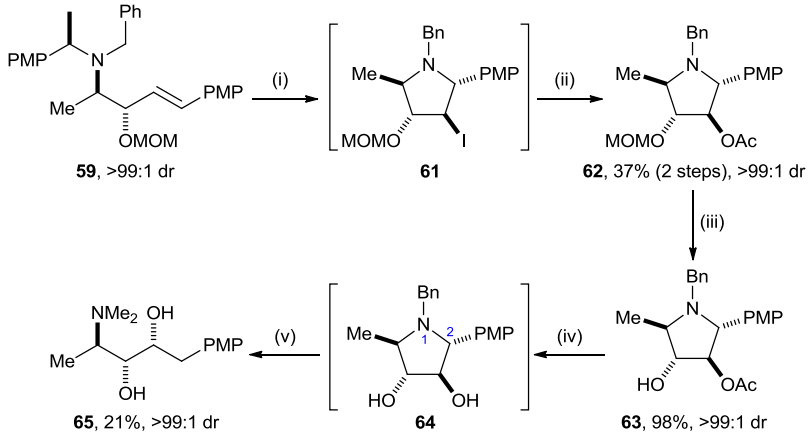
Due to the problematic nature of the N-debenzylation step, it was decided that changing the nature of the substrate from the



Scheme 9. Reagents and conditions: (i) MOMCl, NaH, DMF, 0 °C, 30 min, then rt, 12 h; (ii) DIBAL-H, CH_2Cl_2, −78 °C, 30 min; (iii) BuLi, $[4\text{-MeOC}_6H_4CH_2PPh_3]^+$ $[Cl]^-$, THF, −78 °C, 30 min, then rt, 12 h [PMP=*p*-methoxyphenyl].



Scheme 11. Reagents and conditions: (i) Ac_2O, pyridine, CH_2Cl_2, rt, 16 h; (ii) $Pd(OH)_2$/C, H_2 (1 atm), MeOH, rt, 8 h; (iii) K_2CO_3, MeOH, rt, 6 h [PMP=*p*-methoxyphenyl].

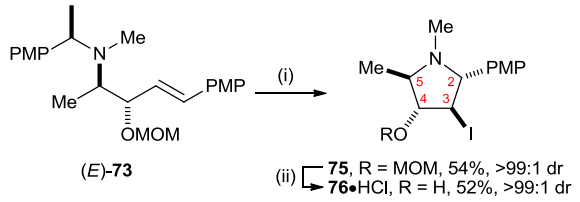


Scheme 10. Reagents and conditions: (i) $NaHCO_3$, I_2, MeCN, rt, 20 h; (ii) AgOAc, AcOH, 30 °C, 24 h; (iii) HCl, MeOH, 50 °C, 5 h; (iv) K_2CO_3, MeOH, rt, 6 h; (v) $Pd(OH)_2$/C, $(CH_2O)_n$, H_2 (1 atm), MeOH, rt, 48 h [PMP=*p*-methoxyphenyl].

N-benzyl substituted compound to the corresponding *N*-methyl substituted analogue (prior to ring-closing iodoamination) would be advantageous as the *N*-methyl group would then be retained throughout the entire synthesis. This approach would then negate the requirement for an N-deprotection step and therefore improve both the atom and step economy of the synthesis. Thus, the conjugate addition of enantiopure lithium amide (*R*)-**69** to *tert*-butyl crotonate **15** gave α-hydroxy-β-amino ester **70** as a single diastereoisomer (>99:1 dr), which was isolated in 71% yield after chromatographic purification. Subsequent protection of the C(2)-hydroxyl group within **70** as the corresponding *O*-MOM ether gave **71** in 70% yield and >99:1 dr. Reduction of the ester functionality within **71** with DIBAL-H, followed by Wittig olefination of the resultant aldehyde **72** gave a mixture of homoallylic amines (*E*)-**73** and (*Z*)-**74**, which were isolated in 57 and 9% yield (over two steps), respectively, and in >99:1 dr in each case (Scheme 12).[26] The configurations of the newly formed double bonds within (*E*)-**73** and (*Z*)-**74** were assigned by ^{1}H NMR ^3J coupling constant analyses, with diagnostic trans [$J_{1,2}$=16.0 Hz for (*E*)-**73**] and cis [$J_{1,2}$=12.0 Hz for (*Z*)-**74**] olefinic coupling constants being observed.

Ring-closing iodoamination was then attempted on homoallylic amine (*E*)-**73**: following our previously optimised procedure,[2] treatment of **73** with I_2 and $NaHCO_3$ in MeCN gave 3-iodopyrrolidine **75** in 54% yield and >99:1 dr. The relative configuration within **75** was unambiguously established by derivatisation to the corresponding alcohol **76** (which was achieved upon treatment with HCl in MeOH), followed by single crystal X-ray diffraction analysis of the corresponding hydrochloride salt **76**·HCl (Scheme 13).[23] These crystallographic data allowed the relative configuration within **76** to be unambiguously assigned, with the absolute (*R*,*R*,*R*,*R*)-configuration within **76** being assigned relative to the known configurations of the C(4) and C(5) stereocentres. Furthermore, the determination of a Flack *x* parameter[24,25] of −0.03(3) for the crystal structure of **76**·HCl allowed its absolute configuration, and therefore also the absolute configurations within **70**–**75**, to be confirmed unambiguously (Fig. 7).

3-Iodopyrrolidine **75** was then treated with AgOAc in AcOH, which gave a 75:25 mixture of **78** (>99:1 dr) and regioisomeric product **79** (>99:1 dr), presumably via the intermediacy of phenonium ion intermediate **77**. Despite exhaustive efforts at purification this mixture proved to be inseparable by flash column chromatography, although there was sufficient resonance dispersion in the ^{1}H NMR spectrum of this mixture (in $CDCl_3$) to allow the relative configurations within both **78** and **79** to be determined by ^{1}H NMR NOE spectroscopic analysis. Subsequently, treating the 75:25 mixture of **78** and **79** with methanolic HCl at 50 °C for 48 h was found to give (−)-codonopsinine **14** in 30% yield (over two steps) and >99:1 dr, after purification of the crude reaction mixture, thus completing the total asymmetric synthesis of this pyrrolidine natural product (Scheme 14).



Scheme 13. Reagents and conditions: (i) $NaHCO_3$, I_2, MeCN, rt, 20 h; (ii) HCl, MeOH, rt, 48 h [PMP=*p*-methoxyphenyl].

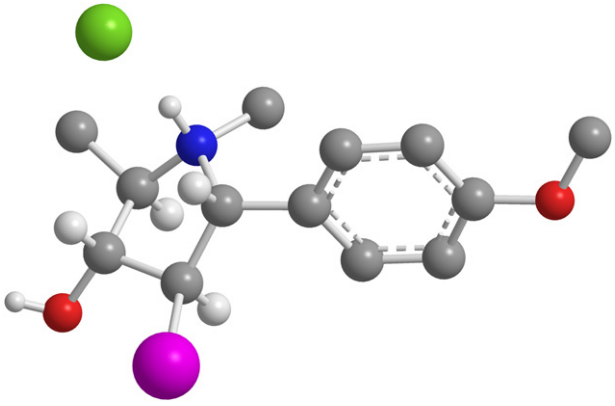
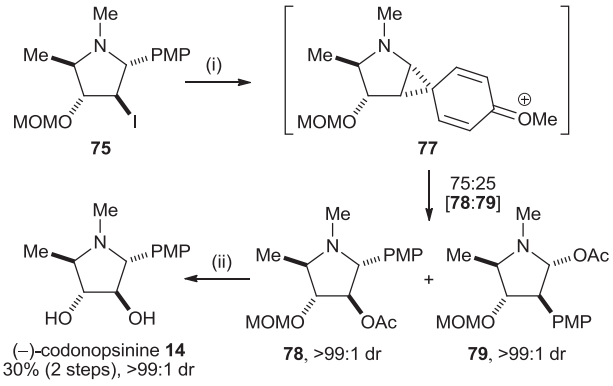
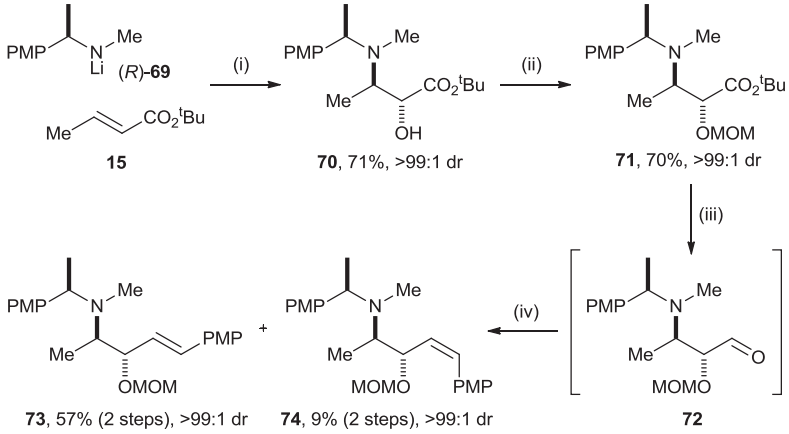


Fig. 7. X-ray crystal structure of **76**·HCl (selected H atoms are omitted for clarity).



Scheme 14. Reagents and conditions: (i) AgOAc, AcOH, 40 °C, 24 h; (ii) HCl, MeOH, 50 °C, 48 h [PMP=*p*-methoxyphenyl].



Scheme 12. Reagents and conditions: (i) THF, −78 °C, 2 h, then (−)-CSO, −78 °C to rt, 12 h; (ii) MOMCl, NaH, DMF, 0 °C, 30 min, then rt, 12 h; (iii) DIBAL-H, CH_2Cl_2, −78 °C, 30 min; (iv) BuLi, $[4\text{-}MeOC_6H_4CH_2PPh_3]^+$ $[Cl]^-$, THF, −78 °C, 30 min, then rt, 12 h [PMP=*p*-methoxyphenyl].

The spectroscopic data for our synthetic sample of (−)-codonopsinine **14** were found to be in excellent agreement with those corresponding to the sample isolated from the natural source {$[\alpha]_D^{20}$ −9.1 (*c* 0.1 in MeOH); lit.[4b] $[\alpha]_D^{20}$ −8.8 (*c* 0.1 in MeOH)} and other samples obtained by total synthesis.[27] Furthermore, recrystallisation of (−)-codonopsinine **14** from pyridine produced colourless plates, which were subjected to X-ray diffraction analysis,[23] unambiguously confirming the relative configuration within codonopsinine **14** (Fig. 8).

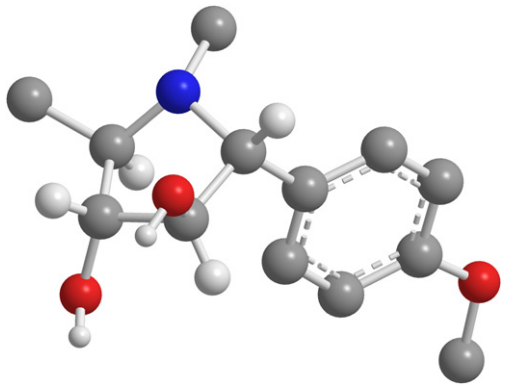


Fig. 8. X-ray crystal structure of (−)-codonopsinine **14** (selected H atoms are omitted for clarity).

3. Conclusion

In summary, the ring-closing iodoamination of (*E*)-configured, *N*-α-methyl-*p*-methoxybenzyl protected homoallylic amines upon treatment with I_2 and $NaHCO_3$ in MeCN occurs with concomitant loss of the *N*-α-methyl-*p*-methoxybenzyl group to give 3-iodopyrrolidines in >99:1 dr. This transformation was used as one of the key steps in the total asymmetric synthesis of (−)-codonopsinine, which was achieved in seven steps (from commercially available *tert*-butyl crotonate) in 5% overall yield and >99:1 dr.

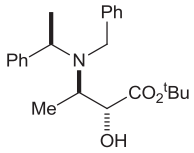
4. Experimental

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 and co-workers.[28] 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.

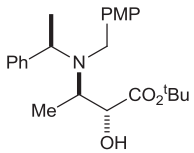
Elemental analyses were recorded by the microanalysis service of the London Metropolitan University, U.K. Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter with a water-jacketed 10 cm cell. Specific 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 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. *tert*-Butyl (*R*,*R*,*R*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]butanoate 25



BuLi (2.4 M, 4.50 mL, 10.9 mmol) was added to a stirred solution of **22**[29] (2.37 g, 11.3 mmol) in THF (30 mL) at −78 °C. The resultant solution was stirred at −78 °C for 30 min before the addition of a solution of **15** (1.00 g, 7.00 mmol) in THF (20 mL) at −78 °C via cannula. The reaction mixture was stirred for 2 h, (−)-CSO[21] (2.74 g, 12.0 mmol) was added and the reaction mixture was allowed to warm to rt over 12 h. The reaction mixture was then quenched with satd aq NH_4Cl (5 mL) and concentrated in vacuo. The residue was partitioned between 10% aq citric acid (50 mL) and CH_2Cl_2 (50 mL) and the aqueous layer was extracted with CH_2Cl_2 (2×50 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (100 mL) and brine (100 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 9:1) gave **25** as a white crystalline solid (1.50 g, 58%, >99:1 dr);[31] mp 85–88 °C; $[\alpha]_D^{20}$ −27.9 (*c* 1.0 in $CHCl_3$); {lit.[31] $[\alpha]_D^{25}$ −34.4 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.08 (3H, d, *J* 7.0, C(4)H_3), 1.32 (3H, d, *J* 6.7, C(α)*Me*), 1.36 (9H, s, CMe_3), 3.02 (1H, br s, O*H*), 3.24–3.27 (1H, m, C(3)*H*), 3.95 (1H, ABd, *J* 15.0, NCH_A), 4.05–4.12 (3H, m, C(α)*H*, C(2)*H*, NCH_B), 7.21–7.36 (8H, m, *Ph*), 7.48 (2H, dd, *J* 7.6, 0.5, *Ph*).

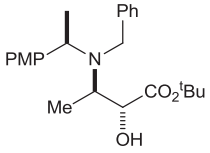
4.3. *tert*-Butyl (*R*,*R*,*R*)-2-hydroxy-3-[*N*-(4′-methoxybenzyl)-*N*-(α-methylbenzyl)amino]butanoate 26



BuLi (2.5 M, 24.1 mL, 60.3 mmol) was added to a stirred solution of **23**[2b] (15.0 g, 62.2 mmol) in THF (150 mL) at −78 °C. The resultant solution was stirred at −78 °C for 30 min before the addition of a solution of **15** (5.50 g, 38.9 mmol) in THF (100 mL) at −78 °C. The

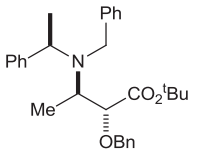
reaction mixture was stirred for 2 h, (−)-CSO[21] (15.1 g, 66.1 mmol) was added and the reaction mixture was allowed to warm to rt over 12 h. The reaction mixture was then quenched with satd aq NH_4Cl (25 mL) and concentrated in vacuo. The residue was partitioned between 10% aq citric acid (150 mL) and CH_2Cl_2 (150 mL) and the aqueous layer was extracted with CH_2Cl_2 (2×150 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (300 mL) and brine (300 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 3:1) gave **26** as a colourless oil (12.4 g, 80%, >99:1 dr); $[\alpha]_D^{20}$ −7.2 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2922 (C–H), 1718 (C=O); δ_H (400 MHz, $CDCl_3$) 1.10 (3H, d, *J* 7.1, C(4)H_3), 1.33 (3H, d, *J* 6.8, C(α)*Me*), 1.38 (9H, s, CMe_3), 3.22–3.26 (1H, m, C(3)*H*), 3.81 (1H, ABd, *J* 14.4, NCH_A), 3.82 (3H, s, O*Me*), 3.88 (1H, ABd, *J* 14.4, NCH_B), 3.93 (1H, d, *J* 2.8, C(2)*H*), 4.02 (1H, q, *J* 6.8, C(α)*H*), 6.87–6.92 (2H, m, C(3′)*H*, C(5′)*H*), 7.18–7.23 (1H, m, *Ph*), 7.28–7.34 (4H, m, *Ph*), 7.36–7.41 (2H, m, C(2′)*H*, C(6′)*H*); δ_C (100 MHz, $CDCl_3$) 12.6 (*C*(4)), 15.7 (C(α)*Me*), 27.8 (CMe_3), 50.0 (NCH_2), 53.9 (*C*(3)), 55.3 (O*Me*), 57.2 (*C*(α)), 73.6 (*C*(2)), 81.9 (*C*Me$_3$), 113.6 (*C*(3′), *C*(5′)), 126.7 (*p*-*Ph*), 127.8, 128.1 (*o*,*m*-*Ph*), 129.5 (*C*(2′), *C*(6′)), 131.2, 134.0 (*i*-*Ph*, *C*(1′)), 158.3 (*C*(4′)), 173.7 (*C*(1)); *m*/*z* (ESI$^+$) 400 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{34}NO_4^+$ ([M+H]$^+$) requires 400.2482; found 400.2477.

4.4. *tert*-Butyl (*R*,*R*,*R*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methyl-4′-methoxybenzyl)amino]butanoate 27



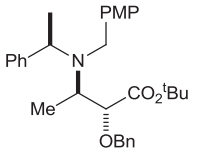
BuLi (2.4 M, 7.60 mL, 18.5 mmol) was added to a stirred solution of **24**[30] (4.61 g, 19.1 mmol) in THF (70 mL) at −78 °C. The resultant solution was stirred at −78 °C for 30 min before the addition of a solution of **15** (1.70 g, 11.9 mmol) in THF (30 mL) at −78 °C. The reaction mixture was stirred for 2 h, (−)-CSO[21] (4.66 g, 20.3 mmol) was added and the reaction mixture was allowed to warm to rt over 12 h. The reaction mixture was then quenched with satd aq NH_4Cl (15 mL) and concentrated in vacuo. The residue was partitioned between 10% aq citric acid (50 mL) and CH_2Cl_2 (50 mL) and the aqueous layer was extracted with CH_2Cl_2 (2×50 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (100 mL) and brine (100 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 2:1) gave **27** as a white crystalline solid (3.91 g, 82%, >99:1 dr); $C_{24}H_{33}NO_4$ requires C, 72.15; H, 8.3; N, 3.5%; found C, 72.3; H, 8.2; N, 3.45%; mp 60–62 °C; $[\alpha]_D^{20}$ −8.4 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2917 (C–H), 1721 (C=O); δ_H (400 MHz, $CDCl_3$) 1.10 (3H, d, *J* 7.1, C(4)H_3), 1.32 (3H, d, *J* 7.0, C(α)*Me*), 1.39 (9H, s, CMe_3), 3.25–3.29 (1H, m, C(3)*H*), 3.79 (3H, s, O*Me*), 3.87 (1H, ABd, *J* 14.7, NCH_A), 3.96 (1H, ABd, *J* 14.7, NCH_B), 3.97 (1H, d, *J* 2.8, C(2)*H*), 3.98 (1H, q, *J* 7.0, C(α)*H*), 6.82–6.86 (2H, m, C(3′)*H*, C(5′)*H*), 7.22–7.37 (5H, m, *Ph*), 7.47–7.50 (2H, m, C(2′)*H*, C(6′)*H*); δ_C (100 MHz, $CDCl_3$) 12.6 (*C*(4)), 16.1 (C(α)*Me*), 28.0 (CMe_3), 50.7 (NCH_2), 53.9 (*C*(3)), 55.2 (O*Me*), 57.0 (*C*(α)), 73.6 (*C*(2)), 82.0 (*C*Me$_3$), 113.5 (*C*(3′), *C*(5′)), 126.6 (*p*-*Ph*), 127.8, 128.1, 129.5 (*C*(2′), *C*(6′), *o*,*m*-*Ph*), 136.3, 142.2 (*i*-*Ph*, *C*(1′)), 158.4 (*C*(4′)), 173.8 (*C*(1)); *m*/*z* (ESI$^+$) 400 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{34}NO_4^+$([M+H]$^+$) requires 400.2482; found 400.2482.

4.5. *tert*-Butyl (*R*,*R*,*R*)-2-benzyloxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]butanoate 28



A solution of **25** (1.49 g, 4.03 mmol) in THF (30 mL) was added to a stirred slurry of NaH (60% dispersion in mineral oil, 170 mg, 4.25 mmol) in THF (20 mL) at 0 °C. The resultant mixture was allowed to warm to rt and stirred for 1 h. BnBr (753 mg, 4.39 mmol) was then added dropwise and the reaction mixture was stirred for a further 12 h before satd aq NH_4Cl (15 mL) was added. The organic layer was washed with brine (50 mL) and the aqueous layer was then extracted with Et_2O (3×50 mL). The combined organic layers were then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 9:1) gave **28** as a colourless oil (1.21 g, 65%, >99:1 dr); $[\alpha]_D^{23}$ +36.6 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2917 (C–H), 1738 (C=O); δ_H (400 MHz, $CDCl_3$) 1.17 (3H, d, *J* 6.9, C(4)H_3), 1.32 (3H, d, *J* 6.9, C(α)*Me*), 1.42 (9H, s, CMe_3), 3.35 (1H, qd, *J* 6.9, 3.5, C(3)*H*), 3.81 (1H, ABd, *J* 14.7, NCH_A), 3.83 (1H, d, *J* 3.5, C(2)*H*), 3.96 (1H, q, *J* 6.9, C(α)*H*), 4.08 (1H, ABd, *J* 14.7, NCH_B), 4.32 (1H, d, *J* 11.3, OCH_A), 4.63 (1H, d, *J* 11.3, OCH_B), 7.19–7.40 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.9 (*C*(4)), 17.8 (C(α)*Me*), 28.0 (CMe_3), 50.6 (NCH_2), 54.5 (*C*(3)), 58.9 (*C*(α)), 72.3 (OCH_2), 80.9 (*C*Me$_3$), 82.0 (*C*(2)), 126.6 (*p*-*Ph*), 127.6, 128.0, 128.8 (*o*,*m*-*Ph*), 137.8, 142.5, 144.4 (*i*-*Ph*), 171.2 (*C*(1)); *m*/*z* (ESI$^+$) 482 ([M+Na]$^+$, 100%), 460 ([M+H]$^+$, 94%); HRMS (ESI$^+$) $C_{30}H_{38}NO_3^+$ ([M+H]$^+$) requires 460.2846; found 460.2845.

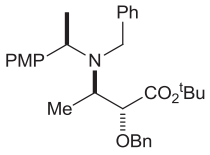
4.6. *tert*-Butyl (*R*,*R*,*R*)-2-benzyloxy-3-[*N*-(4′-methoxybenzyl)-*N*-(α-methylbenzyl)amino]butanoate 29



A solution of **26** (11.6 g, 28.9 mmol) in THF (150 mL) was added to a stirred slurry of NaH (60% dispersion in mineral oil, 1.22 g, 50.7 mmol) in THF (100 mL) at 0 °C. The resultant mixture was allowed to warm to rt and stirred for 1 h. BnBr (5.40 g, 31.6 mmol) was then added dropwise and the reaction mixture was stirred for a further 12 h before satd aq NH_4Cl (50 mL) was added. The organic layer was washed with brine (250 mL) and the aqueous layer was then extracted with Et_2O (3×250 mL). The combined organic layers were then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 9:1) gave **29** as a colourless oil (11.1 g, 78%, >99:1 dr); $C_{31}H_{39}NO_4$ requires C, 76.0; H, 8.0; N, 2.9%; found C, 75.9; H, 7.9; N, 2.7%; $[\alpha]_D^{20}$ +30.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2973 (C–H), 1738 (C=O); δ_H (400 MHz, $CDCl_3$) 1.13 (3H, d, *J* 7.1, C(4)H_3), 1.29 (3H, d, *J* 7.0, C(α)*Me*), 1.39 (9H, s, CMe_3), 3.33–3.35 (1H, m, C(3)*H*), 3.75 (1H, d, *J* 3.8, C(2)*H*), 3.76 (1H, ABd, *J* 14.7, NCH_A), 3.82 (3H, s, O*Me*), 3.94 (1H, ABd, *J* 14.7, NCH_B), 3.95 (1H, q, *J* 7.0, C(α)*H*), 4.30 (1H, ABd, *J* 11.4, OCH_A), 4.60 (1H, ABd, *J* 11.4, OCH_B), 6.84–6.87 (2H, m, C(3′)*H*, C(5′)*H*), 7.27–7.35 (12H, m, *Ph*, C(2′)*H*, C(6′)*H*); δ_C (100 MHz, $CDCl_3$) 12.8 (*C*(4)), 17.4 (C(α)*Me*), 28.1 (CMe_3), 49.9 (NCH_2), 54.3 (*C*(3)), 55.2 (O*Me*), 58.5 (*C*(α)), 72.3 (OCH_2), 80.9 (*C*(2)), 82.4 (*C*Me$_3$), 113.5 (*C*(3′), *C*(5′)), 126.6 (*p*-*Ph*),

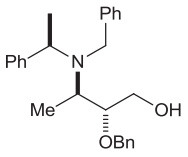
127.6, 128.2, 129.3 (*C*(2′), *C*(6′), *o*,*m*-*Ph*), 134.3, 137.9, 144.4 (*C*(1′), *i*-*Ph*), 158.3 (*C*(4′)), 171.2 (*C*(1)); *m*/*z* (ESI$^+$) 490 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{31}H_{40}NO_4^+$ ([M+H]$^+$) requires 490.2952; found 490.2948.

4.7. *tert*-Butyl (*R*,*R*,*R*)-2-benzyloxy-3-[*N*-benzyl-*N*-(α-methyl-4′-methoxybenzyl)amino]butanoate 30



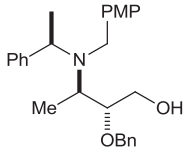
A solution of **27** (2.53 g, 6.34 mmol) in THF (50 mL) was added to a stirred slurry of NaH (60% dispersion in mineral oil, 266 mg, 11.1 mmol) in THF (30 mL) at 0 °C. The resultant mixture was allowed to warm to rt and stirred for 1 h. BnBr (1.18 g, 6.91 mmol) was then added dropwise and the reaction mixture was stirred for a further 12 h before satd aq NH_4Cl (20 mL) was added. The organic layer was washed with brine (60 mL) and the aqueous layer was then extracted with Et_2O (3×50 mL). The combined organic layers were then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 9:1) gave **30** as a colourless oil (1.82 g, 59%, >99:1 dr); $[\alpha]_D^{20}$ +39.8 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2917 (C–H), 1737 (C=O); δ_H (400 MHz, $CDCl_3$) 1.15 (3H, d, *J* 7.1, C(4)H_3), 1.29 (3H, d, *J* 6.8, C(α)*Me*), 1.42 (9H, s, CMe_3), 3.36–3.38 (1H, m, C(3)*H*), 3.80 (1H, d, *J* 1.1, C(2)*H*), 3.81 (1H, ABd, *J* 14.9, NCH_A), 3.82 (3H, s, O*Me*), 3.91 (1H, q, *J* 6.8, C(α)*H*), 4.02 (1H, ABd, *J* 14.9, NCH_B), 4.32 (1H, ABd, *J* 11.1, OCH_A), 4.62 (1H, ABd, *J* 11.1, OCH_B), 6.82–6.86 (2H, m, C(3′)*H*, C(5′)*H*), 7.21–7.34 (10H, m, *Ph*), 7.39–7.42 (2H, m, C(2′)*H*, C(6′)*H*); δ_C (100 MHz, $CDCl_3$) 12.9 (*C*(4)), 17.8 (C(α)*Me*), 28.1 (CMe_3), 50.6 (NCH_2), 54.3 (*C*(3)), 55.2 (O*Me*), 58.2 (*C*(α)), 72.4 (*C*(2)), 80.9 (OCH_2), 82.2 (CMe_3), 113.4 (*C*(3′), *C*(5′)), 126.4 (*p*-*Ph*), 127.7, 128.2, 128.8 (*C*(2′), *C*(6′), *o*,*m*-*Ph*), 136.4, 137.8, 142.5 (*C*(1′), *i*-*Ph*), 158.3 (*C*(4′)), 171.2 (*C*(1)); *m*/*z* (ESI$^+$) 490 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{31}H_{40}NO_4^+$ ([M+H]$^+$) requires 490.2952; found 490.2940.

4.8. (*R*,*R*,*R*)-2-Benzyloxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]butan-1-ol 31



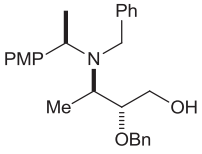
$LiAlH_4$ (111 mg, 2.93 mmol) was added portionwise to a stirred solution of **28** (1.22 g, 2.66 mmol) in THF (15 mL) at 0 °C and the resultant mixture was allowed to warm to rt and stirred for 16 h. The reaction mixture was then cooled to 0 °C and ice/cold EtOAc was added to excess. The reaction mixture was then stirred for 1 h and filtered through Celite® (eluent Et_2O). The filtrate was then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 1:1) gave **31** as a colourless oil (895 mg, 87%, >99:1 dr); $[\alpha]_D^{20}$ +3.8 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3440 (O–H), 2872 (C–H), 2972 (C–H); δ_H (400 MHz, $CDCl_3$) 1.30 (3H, d, *J* 6.7, C(α)*Me*), 1.44 (3H, d, *J* 6.7, C(4)H_3), 3.02 (1H, br s, O*H*), 3.08–3.12 (2H, m, NCH_2), 3.24 (1H, dt, *J* 6.7, 3.2, C(3)*H*), 3.50 (1H, app s, C(2)*H*), 3.77 (1H, app d, *J* 13.3, C(1)H_A), 3.84 (1H, app d, *J* 13.3, C(1)H_B), 3.97 (1H, d, *J* 6.7, C(α)*H*), 4.44 (1H, d, *J* 11.3, OCH_A), 4.56 (1H, d, *J* 11.3, OCH_B), 7.22–7.42 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.0 (C(α)*Me*), 14.4 (*C*(4)), 51.0 (NCH_2), 54.1 (*C*(3)), 57.0 (*C*(α)), 63.1 (*C*(1)), 72.7 (OCH_2), 81.1 (*C*(2)), 127.3, 127.8, 128.0, 128.7, 129.4 (*o*,*m*,*p*-*Ph*), 138.5, 140.0, 143.3 (*i*-*Ph*); *m*/*z* (ESI$^+$) 412 ([M+Na]$^+$, 76%), 390 ([M+H]$^+$, 74%); HRMS (ESI$^+$) $C_{26}H_{32}NO_2^+$ ([M+H]$^+$) requires 390.2428; found 390.2427.

4.9. (*R*,*R*,*R*)-2-Benzyloxy-3-[*N*-(4′-methoxybenzyl)-*N*-(α-methylbenzyl)amino]butan-1-ol 32



$LiAlH_4$ (945 mg, 24.9 mmol) was added portionwise to a stirred solution of **29** (11.1 g, 22.6 mmol) in THF (250 mL) at 0 °C and the resultant mixture was allowed to warm to rt and stirred for 16 h. The reaction mixture was then cooled to 0 °C and ice/cold EtOAc was added to excess. The reaction mixture was then stirred for 1 h and filtered through Celite® (eluent Et_2O). The filtrate was then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O doped with 1% Et_3N, 1:1) gave **32** as a colourless oil (7.30 g, 77%, >99:1 dr); $C_{27}H_{33}NO_3$ requires C, 77.3; H, 7.9; N, 3.3%; found C, 77.3; H, 7.9; N, 3.2%; $[\alpha]_D^{20}$ +18.4 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2970 (C–H); δ_H (400 MHz, $CDCl_3$) 1.29 (3H, d, *J* 7.1, C(4)H_3), 1.43 (3H, d, *J* 7.1, C(α)*Me*), 3.01–3.04 (1H, m, C(1)H_A), 3.07–3.10 (1H, m, C(3)*H*), 3.22–3.25 (1H, m, C(2)*H*), 3.48–3.51 (1H, m, C(1)H_B), 3.69 (1H, ABd, *J* 13.1, NCH_A), 3.84 (3H, s, O*Me*), 3.77 (1H, ABd, *J* 13.1, NCH_B), 3.97 (1H, q, *J* 7.1, C(α)*H*), 4.33 (1H, ABd, *J* 11.4, OCH_A), 4.55 (1H, ABd, *J* 11.4, OCH_B), 6.89–6.93 (2H, m, C(3′)*H*, C(5′)*H*), 7.19–7.36 (12H, m, C(2′)*H*, C(6′)*H*, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.4 (C(α)*Me*), 14.4 (*C*(4)), 50.2 (NCH_2), 54.2 (*C*(3)), 55.3 (O*Me*), 56.5 (*C*(α)), 63.1 (*C*(1)), 72.7 (OCH_2), 80.7 (*C*(2)), 113.9 (*C*(3′), *C*(5′)), 126.6 (*p*-*Ph*), 127.1, 128.0, 128.3 (*C*(2′), *C*(6′), *o*,*m*-*Ph*), 130.5, 138.2, 139.5 (*C*(1′), *i*-*Ph*), 158.2 (*C*(4′)); *m*/*z* (ESI$^+$) 420 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{34}NO_3^+$ ([M+H]$^+$) requires 420.2533; found 420.2525.

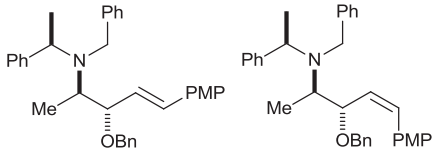
4.10. (*R*,*R*,*R*)-2-Benzyloxy-3-[*N*-benzyl-*N*-(α-methyl-4′-methoxybenzyl)amino]butan-1-ol 33



$LiAlH_4$ (156 mg, 4.09 mmol) was added portionwise to a stirred solution of **30** (1.82 g, 3.72 mmol) in THF (25 mL) at 0 °C and the resultant mixture was allowed to warm to rt and stirred for 16 h. The reaction mixture was then cooled to 0 °C and ice/cold EtOAc was added to excess. The reaction mixture was then stirred for 1 h and filtered through Celite® (eluent Et_2O). The filtrate was then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O doped with 1% Et_3N, 1:1) gave **33** as a colourless oil (1.01 g, 65%, >99:1 dr); $C_{27}H_{33}NO_3$ requires C, 77.3; H, 7.9; N, 3.3%; found C, 77.2; H, 8.0; N, 3.2%; $[\alpha]_D^{20}$ +16.1 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2970 (C–H); δ_H (400 MHz, $CDCl_3$) 1.30 (3H, d, *J* 6.6, C(4)H_3), 1.41 (3H, d, *J* 7.1, C(α)*Me*), 3.08–3.10 (1H, m, C(1)H_A), 3.10–3.12 (1H, m, C(3)*H*), 3.25–3.29 (1H, m, C(2)*H*),

3.53–3.55 (1H, m, C(1)H_B), 3.75 (1H, ABd, *J* 13.3, NCH_A), 3.79 (3H, s, O*Me*), 3.83 (1H, ABd, *J* 13.3, NCH_B), 3.93 (1H, q, *J* 7.1, C(α)*H*), 4.45 (1H, ABd, *J* 11.4, OCH_A), 4.57 (1H, ABd, *J* 11.4, OCH_B), 6.83–6.86 (2H, m, C(3′)*H*, C(5′)*H*), 7.13–7.16 (2H, m, C(2′)*H*, C(6′)*H*), 7.27–7.42 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.7 (C(α)*Me*), 14.4 (*C*(4)), 50.9 (NCH_2), 54.1 (*C*(3)), 55.2 (O*Me*), 56.1 (*C*(α)), 63.2 (*C*(1)), 72.7 (OCH_2), 80.8 (*C*(2)), 113.5 (*C*(3′), *C*(5′)), 126.6 (*p-Ph*), 127.1, 128.0, 128.3 (*C*(2′), *C*(6′), *o,m-Ph*), 135.1, 138.3, 139.7 (*C*(1′), *i-Ph*), 158.6 (*C*(4′)); *m/z* (ESI$^+$) 420 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{34}NO_3^+$ ([M+H]$^+$) requires 420.2533; found 420.2532.

4.11. (3*S*,4*R*,α*R*,*E*)- and (3*S*,4*R*,α*R*,*Z*)-1-(4′-Methoxyphenyl)-3-benzyloxy-4-[*N*-benzyl-*N*-(α-methylbenzyl)amino]pent-1-ene 37 and 40

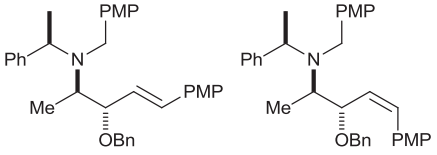


37 **40**

Step 1: DMSO (1.75 mL, 24.7 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (0.85 mL, 10.1 mmol) in CH_2Cl_2 (100 mL) at −78 °C. After 20 min, a solution of **31** (2.18 g, 5.62 mmol) in CH_2Cl_2 (50 mL) at −78 °C was added dropwise. After a further 20 min, Et_3N (4.65 mL, 33.7 mmol) was added and the resultant mixture was stirred for 30 min before being allowed to warm to rt over a period of 30 min. The reaction mixture was then concentrated in vacuo and the residue was partitioned between H_2O (100 mL) and Et_2O (100 mL). The aqueous layer was then extracted with Et_2O (2×100 mL) and the combined organic extracts were dried and concentrated in vacuo to give **34** as a colourless oil (2.03 g); ν_{max} (film) 2973 (C–H), 1728 (C=O); δ_H (400 MHz, $CDCl_3$) 1.25 (3H, d, *J* 3.3, C(4)H_3), 1.38 (3H, d, *J* 7.1, C(α)*Me*), 3.28–3.33 (1H, m, C(3)*H*), 3.40–3.42 (1H, m, C(2)*H*), 3.78 (2H, d, *J* 11.4, NCH_2), 3.86 (1H, q, *J* 7.1, C(α)*H*), 4.31 (1H, d, *J* 11.4, OCH_A), 4.48 (1H, d, *J* 11.4, OCH_B), 7.20–7.36 (15H, m, *Ph*), 8.57 (1H, d, *J* 4.8, C(1)*H*); δ_C (100 MHz, $CDCl_3$) 13.3 (C(α)*Me*), 14.3 (*C*(4)), 50.8 (NCH_2), 50.9 (*C*(3)), 56.2 (*C*(α)), 72.5 (OCH_2), 85.5 (*C*(2)), 127.3 (*p-Ph*), 128.0, 128.7, 129.4 (*o,m-Ph*), 138.5, 140.0, 143.3 (*i-Ph*), 201.2 (*C*(1)); *m/z* (ESI$^+$) 420 ([M+MeOH+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{34}NO_3^+$ ([M+MeOH+H]$^+$) requires 420.2533; found 420.2525.

Step 2: BuLi (2.5 M, 9.48 mL, 23.7 mmol) was added dropwise to a stirred solution of 4-methoxybenzyl triphenylphosphonium chloride[31] (11.5 g, 27.3 mmol) in THF (100 mL) at −78 °C. After 30 min, a solution of **34** (2.03 g) in THF (50 mL) at −78 °C was added. The reaction mixture was then allowed to warm to rt and stirred for 12 h. Satd aq NH_4Cl (30 mL) was then added and the resultant mixture was partitioned between brine (150 mL) and Et_2O (150 mL). The aqueous layer was then extracted with Et_2O (2×150 mL) and the combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 40:1) gave **40** as a colourless oil (401 mg, 15%, >99:1 dr); $C_{34}H_{37}NO_3$ requires C, 83.1; H, 7.6; N, 2.85%; found C, 83.2; H, 7.5; N, 2.8%; $[\alpha]_D^{20}$ +88.6 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2970 (C–H), 1608 (C=C); δ_H (400 MHz, $CDCl_3$) 1.34 (3H, d, *J* 6.6, C(5)H_3), 1.38 (3H, d, *J* 6.9, C(α)*Me*), 3.01–3.04 (1H, m, C(4)*H*), 3.80 (1H, d, *J* 14.4, NCH_A), 3.84 (3H, s, O*Me*), 4.04 (1H, q, *J* 6.9, C(α)*H*), 4.06 (1H, d, *J* 14.4, NCH_B), 4.14 (1H, d, *J* 11.6, OCH_A), 4.38 (1H, d, *J* 11.6, OCH_B), 4.46 (1H, dd, *J* 9.8, 4.7, C(3)*H*), 5.31 (1H, dd, *J* 12.0, 9.8, C(2)*H*), 6.53 (1H, d, *J* 12.0, C(1)*H*), 6.75–6.79 (2H, m, C(3′)*H*, C(5′)*H*), 6.87–6.90 (2H, m, C(2′)*H*, C(6′)*H*), 7.20–7.37 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.8 (*C*(5)), 14.4 (C(α)*Me*), 51.3 (NCH_2), 54.9 (*C*(4)), 55.2 (O*Me*), 56.7 (*C*(α)), 69.7 (OCH_2), 78.8 (*C*(3)), 113.7 (*C*(3′), *C*(5′)), 126.4 (*p-Ph*), 127.8, 128.8, 130.0 (*o,m-Ph*), 130.2 (*C*(2)), 130.7 (*C*(2′), *C*(6′)), 131.6 (*C*(1)), 132.2, 138.8, 142.0, 145.0 (*i-Ph*, *C*(1′)), 158.4 (*C*(4′)); *m/z* (ESI$^+$) 492 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{34}H_{38}NO_3^+$ ([M+H]$^+$) requires 492.2897; found 492.2890. Further elution gave **37** as a colourless oil (701 mg, 25%, >99:1 dr); $[\alpha]_D^{20}$ +129 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2977 (C–H), 1607 (C=C); δ_H (400 MHz, $CDCl_3$) 1.34 (3H, d, *J* 6.6, C(5)H_3), 1.40 (3H, d, *J* 7.0, C(α)*Me*), 3.02–3.06 (1H, m, C(4)*H*), 3.75–3.78 (1H, m, C(3)*H*), 3.87–3.90 (2H, m, NCH_2), 3.90 (3H, s, O*Me*), 3.95 (1H, q, *J* 7.0, C(α)*H*), 4.31 (1H, d, *J* 11.8, OCH_A), 4.56 (1H, d, *J* 11.8, OCH_B), 5.56 (1H, dd, *J* 15.9, 8.3, C(2)*H*), 6.31 (1H, d, *J* 15.9, C(1)*H*), 6.94–6.97 (2H, m, C(3′)*H*, C(5′)*H*), 7.22–7.36 (15H, m, *Ph*), 7.44–7.46 (2H, m, C(2′)*H*, C(6′)*H*); δ_C (100 MHz, $CDCl_3$) 14.8 (*C*(5)), 15.0 (C(α)*Me*), 51.3 (NCH_2), 55.4 (*C*(4)), 55.8 (O*Me*), 57.0 (*C*(α)), 70.7 (OCH_2), 84.3 (*C*(3)), 114.3 (*C*(3′), *C*(5′)), 126.4 (*p-Ph*), 127.8, 128.3, 130.1 (*C*(2), *C*(2′), *C*(6′), *o,m-Ph*), 132.5 (*C*(1)), 139.2, 142.0, 144.7 (*C*(1′), *i-Ph*), 159.6 (*C*(4′)); *m/z* (ESI$^+$) 492 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{34}H_{38}NO_2^+$ ([M+H]$^+$) requires 492.2897; found 492.2888.

4.12. (3*S*,4*R*,α*R*,*E*)- and (3*S*,4*R*,α*R*,*Z*)-1-(4′-Methoxyphenyl)-3-benzyloxy-4-[*N*-(4′′-methoxybenzyl)-*N*-(α-methylbenzyl)-amino]pent-1-ene 38 and 41



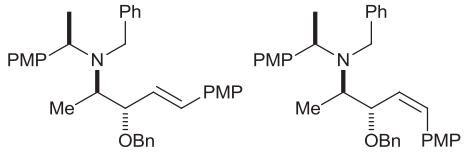
38 **41**

Step 1: DMSO (5.45 mL, 76.8 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (2.66 mL, 31.4 mmol) in CH_2Cl_2 (200 mL) at −78 °C. After 20 min, a solution of **32** (7.30 g, 17.5 mmol) in CH_2Cl_2 (100 mL) at −78 °C was added dropwise. After a further 20 min, Et_3N (14.5 mL, 105 mmol) was added and the resultant mixture was stirred for 30 min before being allowed to warm to rt over a period of 30 min. The reaction mixture was then concentrated in vacuo and the residue was partitioned between H_2O (200 mL) and Et_2O (200 mL). The aqueous layer was then extracted with Et_2O (2×200 mL) and the combined organic extracts were dried and concentrated in vacuo to give **35** as a colourless oil (6.84 g); δ_H (400 MHz, $CDCl_3$) 1.30 (3H, d, *J* 6.6, C(4)H_3), 1.41 (3H, d, *J* 6.9, C(α)*Me*), 3.30–3.32 (1H, m, C(3)*H*), 3.42–3.44 (1H, m, C(2)*H*), 3.73 (2H, s, NCH_2), 3.87 (3H, s, O*Me*), 3.89 (1H, q, *J* 6.9, C(α)*H*), 4.34 (1H, ABd, *J* 11.5, OCH_A), 4.51 (1H, ABd, *J* 11.5, OCH_B), 6.93–6.95 (2H, m, C(3′)*H*, C(5′)*H*), 7.21–7.38 (12H, m, C(2′)*H*, C(6′)*H*, *Ph*), 8.53 (1H, d, *J* 5.1, C(1)*H*); *m/z* (ESI$^+$) 450 ([M+MeOH+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{36}NO_4^+$ ([M+MeOH+H]$^+$) requires 450.2639; found 450.2633.

Step 2: BuLi (2.5 M, 18.0 mL, 45.0 mmol) was added dropwise to a stirred solution of 4-methoxybenzyl triphenylphosphonium chloride[31] (33.8 g, 52.0 mmol) in THF (200 mL) at −78 °C. After 30 min, a solution of **35** (6.84 g) in THF (100 mL) at −78 °C was added. The reaction mixture was then allowed to warm to rt and stirred for 12 h. Satd aq NH_4Cl (50 mL) was then added and the resultant mixture was partitioned between brine (200 mL) and Et_2O (200 mL). The aqueous layer was then extracted with Et_2O (2×200 mL) and the combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave a 66:34 mixture of

38 and **41** as a colourless oil (6.64 g, 71%). Data for **38**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.30 (3H, d, *J* 6.6, C(α)*Me*), 1.36 (3H, d, *J* 6.9, C(5)H_3), 2.98 (1H, app q, *J* 6.9, C(4)*H*), 3.70 (1H, app t, *J* 7.9, C(3)*H*), 4.27 (1H, ABd, *J* 11.7, OCH_A), 5.51 (1H, ABd, *J* 11.7, OCH_B), 5.50 (1H, dd, *J* 15.8, 8.2, C(2)*H*), 6.26 (1H, d, *J* 15.8, C(1)*H*); δ_C (100 MHz, $CDCl_3$) [selected peaks] 54.8 (*C*(4)), 84.0 (*C*(3)), 128.3 (*C*(2)), 132.0 (*C*(1)). Data for **41**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.32 (3H, d, *J* 6.9, C(5)H_3), 1.34 (3H, d, *J* 6.6, C(α)*Me*), 2.98 (1H, dd, *J* 6.9, 6.0, C(4)*H*), 4.14 (1H, ABd, *J* 11.7, OCH_A), 4.37 (1H, ABd, *J* 11.7, OCH_B), 4.41–4.44 (1H, m, C(3)*H*), 5.28 (1H, dd, *J* 12.0, 9.8, C(2)*H*), 6.52 (1H, d, *J* 12.0, C(1)*H*); δ_C (100 MHz, $CDCl_3$) [selected peaks] 54.7 (*C*(4)), 78.9 (*C*(3)), 130.7 (*C*(2)), 131.5 (*C*(1)). Data for mixture: ν_{max} (film) 2967 (C–H), 1607 (C=C); *m*/*z* (ESI^+) 522 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{35}H_{40}NO_3^+$ ($[M+H]^+$) requires 522.3003; found 522.2986.

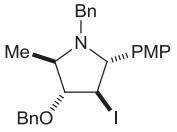
4.13. (3*S*,4*R*,α*R*,*E*)- and (3*S*,4*R*,α*R*,*Z*)-1-(4′-Methoxyphenyl)-3-benzyloxy-4-[*N*-benzyl-*N*-(α-methyl-4″-methoxybenzyl)-amino]pent-1-ene 39 and 42



Step 1: DMSO (0.75 mL, 10.6 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (0.37 mL, 4.35 mmol) in CH_2Cl_2 (50 mL) at −78 °C. After 20 min, a solution of **33** (1.01 g, 2.42 mmol) in CH_2Cl_2 (30 mL) at −78 °C was added dropwise. After a further 20 min, Et_3N (2.01 mL, 14.5 mmol) was added and the resultant mixture was stirred for 30 min before being allowed to warm to rt over a period of 30 min. The reaction mixture was then concentrated in vacuo and the residue was partitioned between H_2O (40 mL) and Et_2O (40 mL). The aqueous layer was then extracted with Et_2O (2×50 mL) and the combined organic extracts were dried and concentrated in vacuo to give **36** as a colourless oil (700 mg); ν_{max} (film) 2971 (C–H), 1728 (C=O); δ_H (400 MHz, $CDCl_3$) 1.26 (3H, d, *J* 6.6, C(4)H_3), 1.35 (3H, d, *J* 7.0, C(α)*Me*), 3.29–3.31 (1H, m, C(3)*H*), 3.38–3.42 (1H, m, C(2)*H*), 3.75 (2H, app s, NCH_2), 3.80 (3H, s, O*Me*), 3.82 (1H, q, *J* 7.0, C(α)*H*), 4.32 (1H, ABd, *J* 11.4, OCH_A), 4.49 (1H, ABd, *J* 11.4, OCH_B), 6.82–6.85 (2H, m, C(3′)*H*, C(5′)*H*), 7.10–7.14 (2H, m, C(2′)*H*, C(6′)*H*), 7.25–7.38 (10H, m, *Ph*), 8.58 (1H, d, *J* 5.1, C(1)*H*); δ_C (100 MHz, $CDCl_3$) 13.3 (C(α)*Me*), 14.4 (*C*(4)), 50.5 (NCH_2), 50.8 (*C*(3)), 55.2 (O*Me*), 55.5 (*C*(α)), 72.5 (OCH_2), 85.6 (*C*(2)), 113.3 (*C*(3′), *C*(5′)), 127.1 (*p*-*Ph*), 128.2, 128.4, 129.2 (*C*(2′), *C*(6′), *o*,*m*-*Ph*), 135.2, 137.2, 140.1 (*C*(1′), *i*-*Ph*), 158.5 (*C*(4′)), 201.2 (*C*(1)); *m*/*z* (ESI^+) 450 ($[M+MeOH+H]^+$, 100%); HRMS (ESI^+) $C_{28}H_{36}NO_4^+$ ($[M+MeOH+H]^+$) requires 450.2639; found 450.2629.

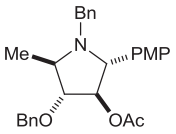
Step 2: BuLi (2.5 M, 3.02 mL, 7.57 mmol) was added dropwise to a stirred solution of 4-methoxybenzyl triphenylphosphonium chloride[31] (3.67 g, 8.75 mmol) in THF (30 mL) at −78 °C. After 30 min, a solution of **36** (700 mg) in THF (20 mL) at −78 °C was added. The reaction mixture was then allowed to warm to rt and stirred for 12 h. Satd aq NH_4Cl (5 mL) was then added and the resultant mixture was partitioned between brine (50 mL) and Et_2O (50 mL). The aqueous layer was then extracted with Et_2O (2×50 mL) and the combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 3:1) gave **42** as a white crystalline solid (190 mg, 15%, >99:1 dr); mp 77–80 °C; $[\alpha]_D^{20}$ +123 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2966 (C–H), 1607 (C=C); δ_H (400 MHz, $CDCl_3$) 1.36 (3H, d, *J* 6.8, C(5)H_3), 1.37 (3H, d, *J* 6.8, C(α)*Me*), 3.02–3.04 (1H, m, C(4)*H*), 3.78 (1H, ABd, *J* 14.2, NCH_A), 3.83 (3H, s, O*Me*), 3.86 (3H, s, O*Me*), 3.98 (1H, q, *J* 6.8, C(α)*H*), 4.13 (1H, ABd, *J* 14.2, NCH_B), 4.17 (1H, d, *J* 11.6, OCH_A), 4.39 (1H, d, *J* 11.6, OCH_B), 4.44 (1H, dd, *J* 10.0, 5.8, C(3)*H*), 5.33 (1H, dd, *J* 12.0, 10.0, C(2)*H*), 6.55 (1H, d, *J* 12.0, C(1)*H*), 6.76–6.81 (2H, m, *Ar*), 6.84–6.88 (4H, m, *Ar*), 7.11–7.15 (2H, m, *Ph*), 7.20–7.24 (4H, m, *Ph*), 7.26–7.32 (4H, m, *Ph*), 7.38–7.44 (2H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 13.3 (C(α)*Me*), 14.3 (*C*(5)), 51.8 (NCH_2), 54.8 (*C*(4)), 55.6 (C(4′)O*Me*, C(4″)O*Me*), 56.3 (*C*(α)), 70.2 (OCH_2), 79.6 (*C*(3)), 113.6, 114.1 (*C*(3′), *C*(5′), *C*(3″), *C*(5″)), 126.9 (*p*-*Ph*), 127.8, 128.8, 130.0 (*C*(2′), *C*(6′), *C*(2″), *C*(6″), *o*,*m*-*Ph*), 131.1 (*C*(2)), 132.0 (*C*(1)), 137.5, 139.2, 142.5 (*C*(1′), *C*(1″), *i*-*Ph*), 158.5, 158.9 (*C*(4′), *C*(4″)); *m*/*z* (ESI^+) 522 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{35}H_{40}NO_3^+$ ($[M+H]^+$) requires 522.3003; found 522.2997. Further elution gave a 62:38 mixture of **39** and **42** (63 mg, 5%). Further elution gave **39** as a colourless oil (355 mg, 28%, >99:1 dr); $[\alpha]_D^{20}$ +153 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2960 (C–H), 1608 (C=C); δ_H (400 MHz, $CDCl_3$) 1.36 (3H, d, *J* 6.8, C(5)H_3), 1.37 (3H, d, *J* 6.8, C(α)*Me*), 3.02–3.04 (1H, m, C(4)*H*), 3.78 (1H, app t, *J* 8.3, C(3)*H*), 3.81 (3H, s, O*Me*), 3.85 (2H, s, NCH_2), 3.86–3.90 (1H, m, C(α)*H*), 3.89 (3H, s, O*Me*), 4.30 (1H, d, *J* 11.9, OCH_A), 4.54 (1H, d, *J* 11.9, OCH_B), 5.54 (1H, dd, *J* 16.1, 8.3, C(2)*H*), 6.31 (1H, d, *J* 16.1, C(1)*H*), 6.77–6.96 (4H, m, C(3′)*H*, C(3″)*H*, C(5′)*H*, C(5″)*H*), 7.16–7.45 (14H, m, C(2′)*H*, C(2″)*H*, C(6′)*H*, C(6″)*H*, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.8, 14.9 (*C*(5), C(α)*Me*), 51.2 (NCH_2), 55.0 (*C*(4)), 55.6, 55.8 (C(4′)O*Me*, C(4″)O*Me*), 56.3 (*C*(α)), 70.7 (OCH_2), 84.4 (*C*(3)), 113.5, 114.3 (*C*(3′), *C*(5′), *C*(3″), *C*(5″)), 127.0 (*p*-*Ph*), 127.8, 128.7, 130.5 (*C*(2′), *C*(6′), *C*(2″), *C*(6″), *o*,*m*-*Ph*), 128.5 (*C*(2)), 132.5 (*C*(1)), 136.8, 139.2, 142.0 (*C*(1′), *C*(1″), *i*-*Ph*), 158.5, 159.6 (*C*(4′), *C*(4″)); *m*/*z* (ESI^+) 522 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{35}H_{40}NO_3^+$ ($[M+H]^+$) requires 522.3003; found 522.2995.

4.14. (*R*,*R*,*R*,*R*)-*N*(1)-Benzyl-2-(4′-methoxyphenyl)-3-iodo-4-benzyloxy-5-methylpyrrolidine 45



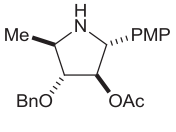
$NaHCO_3$ (48 mg, 0.57 mmol) and I_2 (146 mg, 0.57 mmol) were added to a stirred solution of **39** (100 mg, 0.19 mmol) in MeCN (10 mL) at −20 °C. After stirring for 2 h at −20 °C, the reaction mixture was allowed to warm to rt over 20 h then diluted with Et_2O (20 mL). The resultant mixture was washed with satd aq $Na_2S_2O_3$ (15 mL) then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 3:1) gave **45** as a colourless oil (40 mg, 41%, >99:1 dr); $[\alpha]_D^{20}$ +0.7 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2962 (C–H); δ_H (400 MHz, $CDCl_3$) 1.11 (3H, d, *J* 6.8, C(5)*Me*), 3.38 (1H, ABd, *J* 14.2, NCH_A), 3.48–3.50 (1H, m, C(5)*H*), 3.65 (1H, ABd, *J* 14.2, NCH_B), 3.83 (3H, s, O*Me*), 4.05 (1H, dd, *J* 8.3, 4.1, C(3)*H*), 4.14 (1H, dd, *J* 4.1, 2.5, C(4)*H*), 4.17 (1H, d, *J* 8.3, C(2)*H*), 4.63 (1H, ABd, *J* 12.0, OCH_A), 4.70 (1H, ABd, *J* 12.0, OCH_B), 6.90–6.94 (2H, m, C(3′)*H*, C(5′)*H*), 7.21–7.38 (10H, m, *Ph*), 7.44–7.47 (2H, m, C(2′)*H*, C(6′)*H*); δ_C (100 MHz, $CDCl_3$) 13.3 (C(5)*Me*), 35.2 (*C*(3)), 50.7 (NCH_2), 55.7 (O*Me*), 60.0 (*C*(5)), 72.1 (OCH_2), 75.2 (*C*(2)), 93.7 (*C*(4)), 114.5 (*C*(3′), *C*(5′)), 127.2 (*p*-*Ph*), 128.1, 128.4, 128.7 (*C*(2′), *C*(6′), *o*,*m*-*Ph*), 129.6, 131.6, 139.4 (*i*-*Ph*, *C*(1′)), 155.0 (*C*(4′)); *m*/*z* (ESI^+) 514 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{26}H_{29}INO_2^+$ ($[M+H]^+$) requires 514.1237; found 514.1235.

4.15. (*R*,*R*,*R*,*R*)-*N*(1)-Benzyl-2-(4′-methoxyphenyl)-3-acetoxy-4-benzyloxy-5-methylpyrrolidine 54



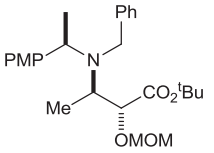
AgOAc (91 mg, 0.48 mmol) was added to a stirred solution of **45** (92 mg, 0.16 mmol) in AcOH (1 mL) and the resultant mixture was heated at 30 °C for 24 h, then allowed to cool to rt. The mixture was then partitioned between satd aq $NaHCO_3$ (10 mL) and CH_2Cl_2 (10 mL) and the organic layer was dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 3:1) gave **54** as a colourless oil (26 mg, 34%, >99:1 dr); $[\alpha]_D^{20}$ +5.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2964 (C–H), 1741 (C=O); δ_H (400 MHz, $CDCl_3$) 1.09 (3H, d, *J* 6.6, C(5)*Me*), 2.06 (3H, s, CO*Me*), 3.36 (1H, ABd, *J* 14.2, NCH_A), 3.42 (1H, qd, *J* 6.6, 2.2, C(5)*H*), 3.64 (1H, app d, *J* 2.2, C(4)*H*), 3.68 (1H, ABd, *J* 14.2, NCH_B), 3.81 (3H, s, O*Me*), 3.87 (1H, d, *J* 4.7, C(2)*H*), 4.58 (1H, ABd, *J* 12.3, OCH_A), 4.70 (1H, ABd, *J* 12.3, OCH_B), 5.23 (1H, dd, *J* 4.7, 2.2, C(3)*H*), 6.88 (2H, d, *J* 8.8, C(3′)*H*, C(5′)*H*), 7.21–7.37 (12H, m, C(2′)*H*, C(6′)*H*, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.6 (C(5)*Me*), 21.2 (CO*Me*), 50.3 (NCH_2), 55.2 (O*Me*), 58.9 (*C*(5)), 69.8 (*C*(2)), 71.2 (OCH_2), 84.4 (*C*(3)), 88.5 (*C*(4)), 113.8 (*C*(3′), *C*(5′)), 126.7 (*p*-*Ph*), 127.9, 128.3, 129.5 (*C*(2′), *C*(6′), *o*,*m*-*Ph*), 138.4 (*i*-*Ph*), 139.3 (*C*(1′)), 159.1 (*C*(4′)), 169.9 (*C*OMe); *m*/*z* (ESI^+) 446 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{28}H_{32}NO_4^+$ ($[M+H]^+$) requires 446.2326; found 446.2311. Further elution gave **55** as a colourless oil (12 mg, 15%, >99:1 dr); $[\alpha]_D^{20}$ +22.2 (*c* 0.5 in $CHCl_3$); ν_{max} (film) 2919 (C–H), 1736 (C=O); δ_H (400 MHz, $CDCl_3$) 0.77 (3H, d, *J* 6.1, C(5)*Me*), 2.12 (3H, s, CO*Me*), 2.99 (1H, app quintet, *J* 6.1, C(5)*H*), 3.24 (1H, ABd, *J* 12.3, NCH_A), 3.32 (1H, app t, *J* 5.7, C(3)*H*), 3.46 (1H, ABd, *J* 12.3, NCH_B), 3.59 (1H, app t, *J* 5.7, C(4)*H*), 3.81 (3H, s, O*Me*), 4.32 (1H, ABd, *J* 11.7, OCH_A), 4.38 (1H, ABd, *J* 11.7, OCH_B), 5.79 (1H, d, *J* 5.7, C(2)*H*), 6.88 (2H, d, *J* 8.5, C(3′)*H*, C(5′)*H*), 7.21–7.37 (12H, m, C(2′)*H*, C(6′)*H*, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.4 (C(5)*Me*), 21.4 (CO*Me*), 55.2 (O*Me*), 61.6 (NCH_2), 66.7 (*C*(5)), 71.3 (OCH_2), 73.0 (*C*(3)), 75.7 (*C*(2)), 78.7 (*C*(4)), 113.7 (*C*(3′), *C*(5′)), 127.8, 128.4, 129.5 (*C*(2′), *C*(6′), *o*,*m*,*p*-*Ph*), 138.0 (*i*-*Ph*), 138.3 (*C*(1′)), 159.4 (*C*(4′)), 170.0 (*C*OMe); *m*/*z* (ESI^+) 446 ($[M+H]^+$, 100%); HRMS (FI^+) $C_{28}H_{31}NO_4^+$ ($[M]^+$) requires 445.2248; found 445.2534. Further elution gave **56** as a colourless oil (5 mg, 6%, >99:1 dr); $[\alpha]_D^{20}$ +5.0 (*c* 0.2 in $CHCl_3$); ν_{max} (film) 2918 (C–H), 1740 (C=O); δ_H (400 MHz, $CDCl_3$) 0.88 (3H, d, *J* 5.7, C(5)*Me*), 1.86 (3H, s, CO*Me*), 2.99 (1H, app quintet, *J* 6.0, C(5)*H*), 3.32 (1H, app t, *J* 5.7, C(4)*H*), 3.41 (1H, dd, *J* 5.7, *J* 7.9, C(3)*H*), 3.60 (1H, ABd, *J* 12.8, NCH_A), 3.81 (3H, s, O*Me*), 3.87 (1H, ABd, *J* 11.7, OCH_A), 3.91 (1H ABd, *J* 12.8, NCH_B), 3.94 (1H, ABd, *J* 11.7, OCH_B), 5.68 (1H, d, *J* 8.2, C(2)*H*), 6.88 (2H, d, *J* 8.8, C(3′)*H*, C(5′)*H*), 7.21–7.37 (12H, m, C(2′)*H*, C(6′)*H*, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.0 (C(5)*Me*), 21.0 (CO*Me*), 55.3 (O*Me*), 62.2 (NCH_2), 66.4 (*C*(5)), 71.2 (OCH_2), 73.3 (*C*(3)), 77.8 (*C*(2)), 79.0 (*C*(4)), 113.8 (*C*(3′), *C*(5′)), 127.0, 127.4, 129.0 (*C*(2′), *C*(6′), *o*,*m*,*p*-*Ph*), 137.8 (*i*-*Ph*), 138.9 (*C*(1′)), 159.7 (*C*(4′)), 170.1 (*C*OMe); *m*/*z* (ESI^+) 446 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{28}H_{32}NO_4^+$ ($[M+H]^+$) requires 446.2326; found 446.2307.

4.16. (*R*,*R*,*R*,*R*)-*N*(1)-2-(4′-Methoxyphenyl)-3-acetoxy-4-benzyloxy-5-methylpyrrolidine 57



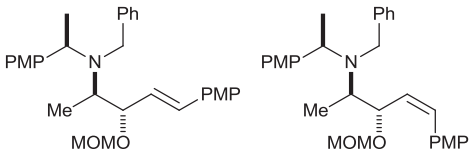
Pd/C (4 mg, 15% w/w with respect to **54**) was added to a stirred solution of **54** (23 mg, 0.05 mmol) in degassed MeOH (1 mL) and placed under an atmosphere of H_2. After 24 h, the mixture was degassed with N_2 and filtered through Celite® (eluent MeOH) before being concentrated in vacuo to give **57** as a colourless oil (16 mg, 87%, >99:1 dr); δ_H (400 MHz, $CDCl_3$) 1.26 (3H, d, *J* 6.7, C(5)*Me*), 2.09 (3H, s, CO*Me*), 3.46–3.51 (1H, m, C(5)*H*), 3.70 (1H, dd, *J* 3.8, 2.1, C(4)*H*), 3.79 (3H, s, O*Me*), 4.25 (1H, d, *J* 3.5, C(2)*H*), 4.57 (1H, ABd, *J* 12.0, OCH_A), 4.70 (1H, s, N*H*), 4.71 (1H, ABd, *J* 12.0, OCH_B), 5.35 (1H, m, C(3)*H*), 6.84–6.88 (2H, m, C(3′)*H*, C(5′)*H*), 7.24–7.35 (5H, m, *Ph*), 7.36–7.38 (2H, m, C(2′)*H*, C(6′)*H*); *m*/*z* (ESI^+) 356 ($[M+H]^+$, 100%).

4.17. *tert*-Butyl (*R*,*R*,*R*)-2-*O*-methoxymethyl-3-[*N*-benzyl-*N*-(α-methyl-4′-methoxybenzyl)amino]butanoate 58



NaH (60% dispersion in mineral oil, 241 mg, 6.02 mmol) was added portionwise to a solution of **27** (2.00 g, 5.01 mmol) in DMF (40 mL) at 0 °C and the resultant mixture was stirred for 30 min at this temperature. MOMCl (484 mg, 6.02 mmol) was added and the resultant mixture was allowed to warm to rt over 12 h. H_2O (100 mL) was then added and the reaction mixture was extracted with Et_2O (2×100 mL). The organic layer was washed with brine (50 mL) then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 8:1) gave **58** as a colourless oil (1.90 g, 86%, >99:1 dr); $[\alpha]_D^{20}$ +9.0 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2975 (C–H), 1739 (C=O); δ_H (400 MHz, $CDCl_3$) 1.12 (3H, d, *J* 7.1, C(4)H_3), 1.28 (3H, d, *J* 6.7, C(α)*Me*), 1.38 (9H, s, CMe_3), 3.29–3.31 (1H, m, C(3)*H*), 3.36 (3H, s, CH_2OMe), 3.79 (3H, s, ArO*Me*), 3.87 (1H, ABd, *J* 14.9, NCH_A), 3.93–3.95 (1H, m, C(α)*H*), 3.95–3.96 (1H, m, C(2)*H*), 3.99 (1H, ABd, *J* 14.9, NCH_B), 4.62 (2H, s, OCH_2), 6.82–6.86 (2H, m, C(3′)*H*, C(5′)*H*), 7.21–7.34 (5H, m, *Ph*), 7.44–7.46 (2H, m, C(2′)*H*, C(6′)*H*); δ_C (100 MHz, $CDCl_3$) 12.7 (*C*(4)), 17.5 (C(α)*Me*), 27.9 (CMe_3), 50.5 (NCH_2), 54.3 (*C*(3)), 55.2 (ArO*Me*), 56.6 (CH_2OMe), 58.4 (*C*(α)), 80.5 (*C*(2)), 80.8 (*C*Me$_3$), 96.8 (OCH_2), 113.4 (*C*(3′), *C*(5′)), 126.4 (*p*-*Ph*), 128.1, 128.2, 128.7 (*C*(2′), *C*(6′), *o*,*m*-*Ph*), 136.4, 142.4 (*C*(1′), *i*-*Ph*), 158.3 (*C*(4′)), 171.1 (*C*(1)); *m*/*z* (ESI^+) 444 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{26}H_{38}NO_5^+$ ($[M+H]^+$) requires 444.2744; found 444.2731.

4.18. (3*S*,4*R*,α*R*,*E*)- and (3*S*,4*R*,α*R*,*Z*)-1-(4′-Methoxyphenyl)-3-*O*-methoxymethyl-4-[*N*-benzyl-*N*-(α-methyl-4″-methoxybenzyl)amino]pent-1-ene 59 and 60

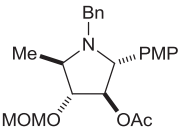


Step 1: DIBAL-H (1.0 M in CH_2Cl_2, 0.86 mL, 0.86 mmol) was added to a stirred solution of **58** (123 mg, 0.28 mmol) in CH_2Cl_2 (19 mL) at −78 °C. After 30 min at this temperature, MeOH (2 mL) was added and the resultant mixture was allowed to warm to rt before satd aq Rochelle's salt (1 mL) was added. The resultant mixture was stirred for 16 h before being filtered through Celite®

(eluent CH_2Cl_2) and the filtrate was dried and concentrated in vacuo to give (*R*,*R*,*R*)-2-*O*-methoxymethyl-3-[*N*-benzyl-*N*-(α-methyl-4′-methoxybenzyl)amino]butanal as a colourless oil (94 mg); δ_H (400 MHz, $CDCl_3$) 1.26 (3H, d, *J* 6.5, C(4)H_3), 1.36 (3H, d, *J* 6.8, C(α)*Me*), 3.26–3.30 (1H, m, C(3)*H*), 3.31 (3H, s, CH_2OMe), 3.34–3.37 (1H, m, C(2)*H*), 3.62 (1H, q, *J* 6.8, C(α)*H*), 3.76 (1H, ABd, *J* 13.7, NCH_A), 3.79 (3H, s, ArO*Me*), 3.82 (1H, ABd, *J* 13.7, NCH_B), 4.52 (1H, ABd, *J* 6.7, OCH_A), 4.58 (1H, ABd, *J* 6.7, OCH_B), 6.82–6.85 (2H, m, C(3′)*H*, C(5′)*H*), 7.11–7.15 (2H, m, C(2′)*H*, C(6′)*H*), 7.24–7.38 (5H, m, *Ph*), 8.64 (1H, d, *J* 4.8, C(1)*H*); *m*/*z* (ESI$^+$) 404 ([M+MeOH+H]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{34}NO_5^+$ ([M+MeOH+H]$^+$) requires 404.2431; found 404.2416.

Step 2: BuLi (2.5 M, 0.58 mL, 1.46 mmol) was added dropwise to a stirred solution of 4-methoxybenzyl triphenylphosphonium chloride[31] (705 mg, 1.68 mmol) in THF (10 mL) at −78 °C. After 30 min, a solution of (*R*,*R*,*R*)-2-*O*-methoxymethyl-3-[*N*-benzyl-*N*-(α-methyl-4′-methoxybenzyl)amino]butanal (94 mg) in THF (5 mL) at −78 °C was added. The reaction mixture was then allowed to warm to rt and stirred for 12 h. Satd aq NH_4Cl (1 mL) was then added and the resultant mixture was partitioned between brine (20 mL) and Et_2O (20 mL). The aqueous layer was then extracted with Et_2O (2×20 mL) and the combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 6:1) gave **60** as a colourless oil (21 mg, 16%, >99:1 dr); $C_{30}H_{37}NO_4$ requires C, 75.8; H, 7.8; N, 2.9%; found C, 75.6; H, 7.6; N, 2.8%; $[\alpha]_D^{20}$ +126 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2930 (C–H), 1605 (C=C); δ_H (400 MHz, $CDCl_3$) 1.27 (3H, d, *J* 6.6, C(5)H_3), 1.31 (3H, d, *J* 6.8, C(α)*Me*), 2.90–2.97 (1H, m, C(4)*H*), 3.28 (3H, s, CH_2OMe), 3.76 (1H, ABd, *J* 13.8, NCH_A), 3.80 (3H, s, ArO*Me*), 3.82 (3H, s, ArO*Me*), 3.90 (1H, q, *J* 6.8, C(α)*H*), 3.96 (1H, ABd, *J* 13.8, NCH_B), 4.45 (1H, d, *J* 6.7, OCH_A), 4.61 (1H, d, *J* 6.7, OCH_B), 4.65 (1H, m, C(3)*H*), 5.12 (1H, dd, *J* 11.9, 10.6, C(2)*H*), 6.43 (1H, d, *J* 11.9, C(1)*H*), 6.84–6.88 (4H, m, *Ar*), 7.00–7.05 (2H, m, *Ar*), 7.20–7.28 (5H, m, *Ph*), 7.34–7.38 (2H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 13.4 (C(α)*Me*), 14.2 (*C*(5)), 51.1 (NCH_2), 54.8 (*C*(4)), 55.2, 55.3, 55.9 (O*Me*), 56.0 (*C*(α)), 80.4 (*C*(3)), 94.2 (OCH_2), 113.1, 113.7 (*C*(3′), *C*(5′), *C*(3″), *C*(5″)), 126.5 (*p*-*Ph*), 128.0, 128.7, 128.8 (*C*(2′), *C*(6′), *C*(2″), *C*(6″), *o*,*m*-*Ph*), 129.9 (*C*(2)), 131.4 (*C*(1)), 136.8, 141.8 (*C*(1′), *C*(1″), *i*-*Ph*), 158.5 (*C*(4′), *C*(4″)); *m*/*z* (ESI$^+$) 476 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{38}NO_4^+$ ([M+H]$^+$) requires 476.2795; found 476.2787. Further elution gave a 50:50 mixture of **59** and **60** (19 mg, 15%). Further elution gave **59** as a colourless oil (50 mg, 39%, >99:1 dr); $[\alpha]_D^{20}$ +123 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2934 (C–H), 1608 (C=C); δ_H (400 MHz, $CDCl_3$) 1.31 (3H, d, *J* 6.6, C(5)H_3), 1.36 (3H, d, *J* 7.1, C(α)*Me*), 2.96–2.98 (1H, m, C(4)*H*), 3.35 (3H, s, CH_2OMe), 3.78–3.83 (4H, m, ArO*Me*, NCH_A), 3.85–3.91 (2H, m, C(α)*H*, NCH_B), 3.86 (3H, s, ArO*Me*), 3.97 (1H, app t, *J* 8.6, C(3)*H*), 4.42 (1H, d, *J* 6.7, OCH_A), 4.69 (1H, d, *J* 6.7, OCH_B), 5.54 (1H, dd, *J* 15.9, 8.6, C(2)*H*), 6.31 (1H, d, *J* 15.9, C(1)*H*), 6.73–6.93 (4H, m, C(3′)*H*, C(5′)*H*, C(3″)*H*, C(5″)*H*), 7.17–7.43 (9H, m, C(2′)*H*, C(6′)*H*, C(2″)*H*, C(6″)*H*, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.0 (C(α)*Me*), 14.8 (*C*(5)), 50.7 (NCH_2), 54.3 (*C*(4)), 55.2, 55.3 (C(4′)O*Me*, C(4″)O*Me*), 55.6 (O*Me*), 55.8 (*C*(α)), 80.4 (*C*(3)), 93.5 (OCH_2), 113.1, 113.8 (*C*(3′), *C*(5′), *C*(3″), *C*(5″)), 126.6 (*p*-*Ph*), 127.4 (*C*(2)), 127.5, 128.1, 129.6 (*C*(2′), *C*(6′), *C*(2″), *C*(6″), *o*,*m*-*Ph*), 132.7 (*C*(1)), 136.3, 141.1 (*C*(1′), *C*(1″), *i*-*Ph*), 159.1 (*C*(4′), *C*(4″)); *m*/*z* (ESI$^+$) 476 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{38}NO_4^+$ ([M+H]$^+$) requires 476.2795; found 476.2779.

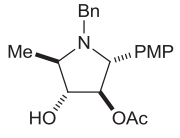
4.19. (*R*,*R*,*R*,*R*)-*N*(1)-Benzyl-2-(4′-methoxyphenyl)-3-acetoxy-4-*O*-methoxymethyl-5-methylpyrrolidine 62



Step 1: $NaHCO_3$ (106 mg, 1.26 mmol) and I_2 (321 mg, 1.26 mmol) were added to a stirred solution of **59** (100 mg, 0.19 mmol) in MeCN (10 mL) at −20 °C. After stirring for 2 h at this temperature, the reaction mixture was allowed to warm to rt and was stirred for a further 20 h. The reaction mixture was then diluted with Et_2O (25 mL), washed with satd aq $Na_2S_2O_3$ (25 mL), and the organic layer was dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 3:1) gave an impure sample of **61** as a colourless oil (109 mg); δ_H (400 MHz, $CDCl_3$) 1.16 (3H, d, *J* 6.8, C(5)*Me*), 3.39 (3H, s, CH_2OMe), 3.39–3.46 (2H, m, C(5)*H*, NCH_A), 3.65 (1H, ABd, *J* 14.4, NCH_B), 3.82 (3H, s, O*Me*), 3.98 (1H, dd, *J* 8.6, 4.8, C(3)*H*), 4.15 (1H, d, *J* 8.6, C(2)*H*), 4.26 (1H, m, C(4)*H*), 4.69 (1H, ABd, *J* 6.8, OCH_A), 4.79 (1H, ABd, *J* 6.8, OCH_B), 6.90–6.94 (2H, m, C(3′)*H*, C(5′)*H*), 7.26–7.37 (5H, m, *Ph*), 7.44–7.48 (2H, m, C(2′)*H*, C(6′)*H*); δ_C (100 MHz, $CDCl_3$) [selected peaks] 12.7 (C(5)*Me*), 35.1 (*C*(3)), 50.3 (NCH_2), 55.3, 55.6 (O*Me*), 59.8 (*C*(5)), 74.4 (*C*(2)), 91.4 (*C*(4)), 95.2 (OCH_2), 113.6, 114.1 (*C*(3′), *C*(5′)), 126.8 (*p*-*Ph*), 127.5, 128.0, 128.5 (*C*(2′), *C*(6′), *o*,*m*-*Ph*); *m*/*z* (ESI$^+$) 468 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{27}INO_3^+$ ([M+H]$^+$) requires 468.1030; found 468.1018.

Step 2: AgOAc (91 mg, 0.48 mmol) was added to a stirred solution of **61** (92 mg) in AcOH (1 mL) and the resultant mixture was heated at 30 °C for 24 h, then allowed to cool to rt. The mixture was then partitioned between satd aq $NaHCO_3$ (10 mL) and CH_2Cl_2 (10 mL) and the organic layer was dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 3:1) gave **62** as a colourless oil (26 mg, 37% from **59**, >99:1 dr); $[\alpha]_D^{20}$ +3.4 (*c* 0.5 in $CHCl_3$); ν_{max} (film) 2932 (C–H), 1744 (C=O); δ_H (400 MHz, C_6D_6) 1.14 (3H, d, *J* 6.8, C(5)*Me*), 1.73 (3H, s, CO*Me*), 3.29 (3H, s, CH_2OMe), 3.39 (1H, ABd, *J* 14.0, NCH_A), 3.41 (3H, s, ArO*Me*), 3.63 (1H, app qd, *J* 6.8, 2.2, C(5)*H*), 3.81 (1H, ABd, *J* 14.0, NCH_B), 4.07 (1H, dd, *J* 2.2, 0.5, C(4)*H*), 4.11 (1H, d, *J* 4.7, C(2)*H*), 4.66 (1H, ABd, *J* 6.8, OCH_A), 4.94 (1H, ABd, *J* 6.8, OCH_B), 5.23 (1H, app ddd, *J* 4.7, 2.2, 1.6, C(3)*H*), 6.91–6.94 (2H, m, C(3′)*H*, C(5′)*H*), 7.25–7.34 (5H, m, *Ph*), 7.58–7.62 (2H, m, C(2′)*H*, C(6′)*H*); δ_C (100 MHz, $CDCl_3$) 12.2 (C(5)*Me*), 21.2 (CO*Me*), 50.3 (NCH_2), 55.3, 55.6 (O*Me*), 59.0 (*C*(5)), 69.6 (*C*(2)), 85.3 (*C*(3)), 86.3 (*C*(4)), 113.9 (*C*(3′), *C*(5′)), 126.7 (*p*-*Ph*), 128.3, 129.5 (*C*(2′), *C*(6′), *o*,*m*-*Ph*), 132.4 (*i*-*Ph*), 139.2 (*C*(1′)), 159.2 (*C*(4′)), 170.0 (*C*OMe); *m*/*z* (ESI$^+$) 400 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{30}NO_5^+$ ([M+H]$^+$) requires 400.2118; found 400.2104.

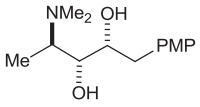
4.20. (*R*,*R*,*R*,*R*)-*N*(1)-Benzyl-2-(4′-methoxyphenyl)-3-acetoxy-4-hydroxy-5-methylpyrrolidine 63



HCl (2.0 M in MeOH, 0.06 mL, 0.12 mmol) was added to a stirred solution of **62** (44 mg, 0.11 mmol) in MeOH (2 mL) and the resultant mixture was heated at 50 °C for 5 h. The mixture was then concentrated in vacuo and the residue was partitioned between satd aq $NaHCO_3$ (5 mL) and CH_2Cl_2 (5 mL). The organic layer was dried and concentrated in vacuo to give **63** as an orange oil (39 mg, 98%, >99:1 dr); $[\alpha]_D^{20}$ +0.9 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2964 (C–H), 1731 (C=O); δ_H (400 MHz, $CDCl_3$) 1.13 (3H, d, *J* 6.6, C(5)*Me*), 2.09 (3H, s, CO*Me*), 3.23 (1H, br s, O*H*), 3.33 (1H, m, C(5)*H*), 3.34 (1H, ABd, *J* 14.1, NCH_A), 3.65 (1H, ABd, *J* 14.1, NCH_B), 3.80 (1H, m, C(4)*H*), 3.82 (3H, s, O*Me*), 3.97 (1H, d, *J* 6.1, C(2)*H*), 4.75 (1H, dd, *J* 6.1, 2.8, C(3)*H*), 6.89–6.92 (2H, m, C(3′)*H*, C(5′)*H*), 7.26–7.36 (7H, m, C(2′)*H*, C(6′)*H*,

Ph); δ_C (100 MHz, $CDCl_3$) 12.7 (C(5)*Me*), 21.0 (CO*Me*), 50.0 (NCH_2), 55.3 (O*Me*), 60.3 (*C*(5)), 68.5 (*C*(2)), 82.5 (*C*(4)), 89.6 (*C*(3)), 114.0 (*C*(3′), *C*(5′)), 126.7 (*p-Ph*), 128.1, 128.3, 129.4 (*C*(2′), *C*(6′), *o,m-Ph*), 131.8 (*i-Ph*), 139.0 (*C*(1′)), 159.3 (*C*(4′)), 172.3 (*C*OMe); *m/z* (ESI^+) 356 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{21}H_{26}NO_4^+$ ($[M+H]^+$) requires 356.1856; found 356.1849.

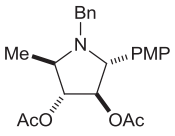
4.21. (*R,R,R*)-1-(4′-Methoxyphenyl)-2,3-dihydroxy-4-(*N,N*-dimethylamino)pentane 65



Step 1: K_2CO_3 (311 mg, 2.25 mmol) was added to a stirred solution of **63** (40 mg, 0.11 mmol) in MeOH (5 mL) at rt. After stirring for 6 h, the mixture was concentrated in vacuo and the residue was partitioned between H_2O (10 mL) and CH_2Cl_2 (10 mL). The organic layer was dried and concentrated in vacuo to give **64** as a colourless oil (34 mg, >99:1 dr); δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.13 (3H, d, *J* 6.8, C(5)*Me*), 3.20–3.25 (1H, m, C(5)*H*), 3.44 (1H, ABd, *J* 14.0, NCH_A), 3.61 (1H, ABd, *J* 14.0, NCH_B), 3.81 (3H, s, O*Me*), 6.88 (2H, d, *J* 8.8, C(3′)*H*, C(5′)*H*), 7.25–7.34 (5H, m, *Ph*), 7.37 (2H, d, *J* 8.5, C(2′)*H*, C(6′)*H*); *m/z* (ESI^+) 314 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{19}H_{24}NO_3^+$ ($[M+H]^+$) requires 314.1751; found 314.1744.

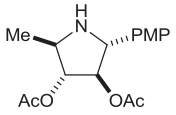
Step 2: Pd(OH)$_2$/C (8 mg, 20% w/w with respect to **64**) was added to a stirred solution of **64** (34 mg, >99:1 dr) and $(CH_2O)_n$ (7 mg, 0.23 mmol) in degassed MeOH (5 mL) under H_2 (5 atm). After 48 h, the mixture was degassed with N_2 and filtered through Celite® (eluent MeOH) before being concentrated in vacuo to give **65** as a colourless oil (6 mg, 21%, >99:1 dr); $[\alpha]_D^{20}$ +5.7 (*c* 0.5 in $CHCl_3$); ν_{max} (film) 2930 (C–H); δ_H (400 MHz, $CDCl_3$) 1.08 (3H, d, *J* 6.6, C(5)H_3), 2.29 (6H, s, N*Me*$_2$), 2.72–2.79 (2H, m, C(1)H_A, C(4)*H*), 2.84 (1H, dd, *J* 13.6, 5.4, C(1)H_B), 3.52 (1H, dd, *J* 6.6, 3.5, C(3)*H*), 3.79 (3H, s, O*Me*), 3.97–4.02 (1H, m, C(2)*H*), 6.83–6.87 (2H, m, C(3′)*H*, C(5′)*H*), 7.17–7.23 (2H, m, C(2′)*H*, C(6′)*H*); δ_C (100 MHz, $CDCl_3$) 8.9 (*C*(5)), 38.6 (*C*(1)), 41.5 (N*Me*$_2$), 55.2 (O*Me*), 61.7 (*C*(4)), 73.0 (*C*(2)), 73.3 (*C*(3)), 113.9 (*C*(3′), *C*(5′)), 130.3 (*C*(2′), *C*(6′)), 130.7 (*C*(1′)), 158.1 (*C*(4′)); *m/z* (ESI^+) 254 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{14}H_{24}NO_3^+$ ($[M+H]^+$) requires 254.1751; found 254.1757.

4.22. (*R,R,R,R*)-*N*(1)-Benzyl-2-(4′-methoxyphenyl)-3,4-diacetoxy-5-methylpyrrolidine 66



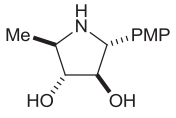
Ac_2O (23 μL, 0.25 mmol) was added to a stirred solution of **63** (44 mg, 0.12 mmol) in pyridine (5 mL) at rt. After 16 h, the mixture was partitioned between CH_2Cl_2 (15 mL) and satd aq Cu_2SO_4 (15 mL). The aqueous layer was extracted with CH_2Cl_2 (2×10 mL) and the combined organic extracts were washed with H_2O (10 mL) and brine (10 mL) before being dried and concentrated in vacuo to give **66** as a colourless oil (41 mg, 83%, >99:1 dr); $[\alpha]_D^{20}$ +4.0 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2930 (C–H), 1742 (C=O); δ_H (400 MHz, $CDCl_3$) 1.16 (3H, d, *J* 6.8, C(5)*Me*), 2.05 (3H, s, CO*Me*), 2.11 (3H, s, CO*Me*), 3.29 (1H, app q, *J* 6.8, C(5)*H*), 3.38 (1H, ABd, *J* 14.1, NCH_A), 3.63 (1H, ABd, *J* 14.1, NCH_B), 3.81 (3H, s, O*Me*), 3.88 (1H, d, *J* 6.1, C(2)*H*), 4.83 (1H, dd, *J* 2.3, 1.8, C(4)*H*), 5.14 (1H, *J* 6.1, 2.3, C(3)*H*), 6.89–6.92 (2H, m, C(3′)*H*, C(5′)*H*), 7.26–7.33 (5H, m, *Ph*), 7.36–7.42 (2H, m, C(2′)*H*, C(6′)*H*); δ_C (100 MHz, $CDCl_3$) 11.0 (C(5)*Me*), 20.9, 21.1 (CO*Me*), 50.0 (NCH_2), 55.3 (O*Me*), 59.3 (*C*(5)), 69.2 (*C*(2)), 82.8 (*C*(4)), 84.0 (*C*(3)), 114.0 (*C*(3′), *C*(5′)), 126.8 (*p-Ph*), 128.1, 128.2, 128.4, 129.2 (*C*(2′), *C*(6′), *o,m-Ph*), 131.8 (*i-Ph*), 138.8 (*C*(1′)), 159.4 (*C*(4′)), 169.6, 170.3 (*C*OMe); *m/z* (ESI^+) 398 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{23}H_{28}NO_5^+$ ($[M+H]^+$) requires 398.1962; found 398.1947.

4.23. (*R,R,R,R*)-*N*(1)-2-(4′-Methoxyphenyl)-3,4-diacetoxy-5-methylpyrrolidine 67



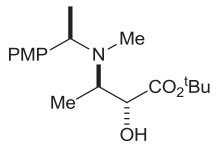
$Pd(OH)_2$/C (8 mg, 20% w/w with respect to **66**) was added to a stirred solution of **66** (40 mg, 0.10 mmol) in degassed MeOH (5 mL) and placed under an atmosphere of H_2. After 8 h, the mixture was degassed with N_2 and filtered through Celite® (eluent MeOH) before being concentrated in vacuo to give **67** as a colourless oil (22 mg, 71%, >99:1 dr); $[\alpha]_D^{20}$ +7.1 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2964 (C–H), 1743 (C=O); δ_H (400 MHz, $CDCl_3$) 1.43 (3H, d, *J* 7.1, C(5)*Me*), 2.09 (3H, s, CO*Me*), 2.12 (3H, s, CO*Me*), 3.47 (1H, br s, N*H*), 3.79 (1H, m, C(5)*H*), 3.80 (3H, s, O*Me*), 4.62 (1H, d, *J* 5.1, C(2)*H*), 4.92 (1H, m, C(4)*H*), 5.36 (1H, dd, *J* 5.1, 2.3, C(3)*H*), 6.87–6.90 (2H, m, C(3′)*H*, C(5′)*H*), 7.43–7.46 (2H, m, C(2′)*H*, C(6′)*H*); δ_C (100 MHz, $CDCl_3$) 15.7 (C(5)*Me*), 20.8, 20.9 (CO*Me*), 55.2 (O*Me*), 59.1 (*C*(5)), 64.8 (*C*(2)), 80.7 (*C*(4)), 81.2 (*C*(3)), 114.4 (*C*(3′), *C*(5′)), 129.4 (*C*(2′), *C*(6′)), 138.8 (*C*(1′)), 160.2 (*C*(4′)), 169.5, 169.9 (*C*OMe); *m/z* (ESI^+) 308 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{16}H_{22}NO_5^+$ ($[M+H]^+$) requires 308.1492; found 308.1486.

4.24. (*R,R,R,R*)-*N*(1)-2-(4′-Methoxyphenyl)-3,4-dihydroxy-5-methylpyrrolidine 68



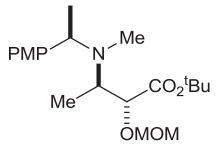
K_2CO_3 (198 mg, 1.43 mmol) was added to a stirred solution of **67** (22 mg, 0.07 mmol) in MeOH (5 mL) at rt. After stirring for 6 h, the mixture was concentrated in vacuo and the residue was partitioned between H_2O (5 mL) and CH_2Cl_2 (5 mL). The aqueous layer was concentrated in vacuo and the residue was dissolved in $CHCl_3$, then dried and concentrated in vacuo to give an impure sample of **68** as a colourless oil (15 mg, >99:1 dr); δ_H (400 MHz, $CDCl_3$) 1.32 (3H, d, *J* 6.5, C(5)*Me*), 2.01 (1H, br s, N*H*), 3.34–3.37 (1H, m, C(5)*H*), 3.78–3.81 (1H, m, C(4)*H*), 3.81 (3H, s, O*Me*), 4.00–4.04 (1H, m, C(3)*H*), 4.08–4.13 (1H, m, C(2)*H*), 6.89 (2H, d, *J* 8.7, C(3′)*H*, C(5′)*H*), 7.35 (2H, d, *J* 8.7, C(2′)*H*, C(6′)*H*); δ_C (100 MHz, $CDCl_3$) 14.1 (C(5)*Me*), 55.3 (O*Me*), 57.3 (*C*(5)), 64.8 (*C*(2)), 83.8 (*C*(4)), 84.9 (*C*(3)), 114.1 (*C*(3′), *C*(5′)), 127.8, 127.9 (*C*(2′), *C*(6′)), 159.1 (*C*(4′));[32] *m/z* (ESI^+) 224 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{12}H_{18}NO_3^+$ ($[M+H]^+$) requires 224.1281; found 224.1280.

4.25. *tert*-Butyl (*R*,*R*,*R*)-2-hydroxy-3-[*N*-methyl-*N*-(α-methyl-4′-methoxybenzyl)amino]butanoate 70



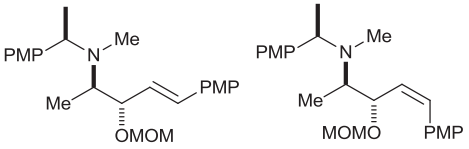
BuLi (2.5 M, 0.59 mL, 1.47 mmol) was added to a stirred solution of (*R*)-*N*-methyl-*N*-(α-methyl-4′-methoxybenzyl)amine[30] (250 mg, 1.52 mmol) in THF (10 mL) at −78 °C. The resultant solution was stirred at −78 °C for 30 min before the addition of a solution of **15** (134 mg, 0.95 mmol) in THF (5 mL) at −78 °C. The reaction mixture was stirred for 2 h, (−)-CSO[21] (369 mg, 1.61 mmol) was added and the reaction mixture was allowed to warm to rt over 12 h. The reaction mixture was then quenched with satd aq NH_4Cl (5 mL) and concentrated in vacuo. The residue was partitioned between 10% aq citric acid (15 mL) and CH_2Cl_2 (15 mL) and the aqueous layer was extracted with CH_2Cl_2 (2×15 mL). The combined organic extracts were washed sequentially 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, 2:1) gave **70** as a colourless oil (221 mg, 71%, >99:1 dr); $[\alpha]_D^{20}$ −23.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3490 (O–H), 2975 (C–H), 1722 (C=O); δ_H (400 MHz, $CDCl_3$) 0.94 (3H, d, *J* 6.8, C(4)H_3), 1.36 (3H, d, *J* 6.6, C(α)*Me*), 1.43 (9H, s, CMe_3), 2.23 (3H, s, N*Me*), 3.15–3.22 (1H, m, C(3)*H*), 3.72 (1H, q, *J* 6.8, C(α)*H*), 3.80 (3H, s, O*Me*), 4.15 (1H, d, *J* 3.8, C(2)*H*), 6.82–6.87 (2H, m, C(3′)*H*, C(5′)*H*), 7.22–7.27 (2H, m, C(2′)*H*, C(6′)*H*); δ_C (100 MHz, $CDCl_3$) 10.8 (*C*(4)), 20.2 (C(α)*Me*), 28.0 (CMe_3), 33.2 (N*Me*), 55.2 (O*Me*), 56.6 (*C*(3)), 61.1 (*C*(α)), 71.8 (*C*(2)), 79.6 (*C*Me_3), 113.6 (*C*(3′), *C*(5′)), 128.5, 128.8 (*C*(2′), *C*(6′)), 136.8 (*C*(1′)), 153.2 (*C*(4′)), 170.7 (*C*(1)); *m*/*z* (ESI^+) 324 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{18}H_{30}NO_4^+$ ($[M+H]^+$) requires 324.2169; found 324.2162.

4.26. *tert*-Butyl (*R*,*R*,*R*)-2-*O*-methoxymethyl-3-[*N*-methyl-*N*-(α-methyl-4′-methoxybenzyl)amino]butanoate 71



NaH (343 mg, 8.58 mmol) was added portionwise to a stirred solution of **70** (2.31 g, 7.15 mmol) in DMF (100 mL) at 0 °C and the resultant mixture was stirred for 30 min at this temperature. MOMCl (690 mg, 8.58 mmol) was added and the resultant mixture was allowed to warm to rt over 16 h. H_2O (100 mL) was added and the resultant mixture was extracted with Et_2O (2×100 mL). The organic layer was washed with brine (50 mL) then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 2:1) gave **71** as a colourless oil (1.84 g, 70%, >99:1 dr); $C_{20}H_{33}NO_5$ requires C, 65.4; H, 9.05; N, 3.8%; found C, 65.5; H, 8.9; N, 3.7%; $[\alpha]_D^{20}$ +9.8 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2976 (C–H), 1740 (C=O); δ_H (400 MHz, $CDCl_3$) 0.97 (3H, d, *J* 6.6, C(4)H_3), 1.31 (3H, d, *J* 6.7, C(α)*Me*), 1.48 (9H, s, CMe_3), 2.06 (3H, s, N*Me*), 3.39 (3H, s, CH_2O*Me*), 3.40 (1H, m, C(3)*H*), 3.54 (1H, q, *J* 6.7, C(α)*H*), 3.80 (3H, s, ArO*Me*), 3.87 (1H, d, *J* 8.1, C(2)*H*), 4.66 (1H, ABd, *J* 6.9, OCH_A), 4.68 (1H, ABd, *J* 6.9, OCH_B), 6.80–6.83 (2H, m, C(3′)*H*, C(5′)*H*), 7.18–7.21 (2H, m, C(2′)*H*, C(6′)*H*); δ_C (100 MHz, $CDCl_3$) 9.2 (*C*(4)), 21.5 (C(α)*Me*), 28.1 (CMe_3), 33.1 (N*Me*), 55.2 (ArO*Me*), 55.9 (CH_2O*Me*), 56.2 (*C*(3)), 62.0 (*C*(α)), 80.6 (*C*Me_3), 81.1 (*C*(2)), 96.8 (OCH_2), 113.4 (*C*(3′), *C*(5′)), 128.5 (*C*(2′), *C*(6′)), 137.7 (*C*(1′)), 158.3 (*C*(4′)), 171.3 (*C*(1)); *m*/*z* (ESI^+) 368 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{20}H_{34}NO_5^+$ ($[M+H]^+$) requires 368.2431; found 368.2422.

4.27. (3*S*,4*R*,α*R*,*E*)- and (3*S*,4*R*,α*R*,*Z*)-1-(4′-Methoxyphenyl)-3-*O*-methoxymethyl-4-[*N*-methyl-*N*-(α-methyl-4″-methoxybenzyl)amino]pent-1-ene 73 and 74

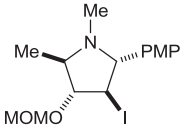


Step 1: DIBAL-H (1.0 M in CH_2Cl_2, 20.3 mL, 20.3 mmol) was added dropwise to a stirred solution of **71** (2.40 g, 6.54 mmol) in CH_2Cl_2 (120 mL) at −78 °C. After stirring at this temperature for 30 min, MeOH (10 mL) was added and the resultant mixture was allowed to warm to rt before satd aq Rochelle's salt (1.5 mL) was added. The resultant mixture was stirred for 16 h before being filtered through Celite® (eluent CH_2Cl_2). The filtrate was then dried and concentrated in vacuo to give **72** as a colourless oil (1.67 g); ν_{max} (film) 2960 (C–H), 1730 (C=O); δ_H (400 MHz, $CDCl_3$) 1.06 (3H, d, *J* 6.3, C(4)H_3), 1.30 (3H, d, *J* 6.8, C(α)*Me*), 2.07 (3H, s, N*Me*), 3.39 (3H, s, CH_2O*Me*), 3.50 (1H, m, C(3)*H*), 3.62 (1H, q, *J* 6.8, C(α)*H*), 3.76 (1H, m, C(2)*H*), 3.80 (3H, s, ArO*Me*), 4.64 (1H, ABd, *J* 6.8, OCH_A), 4.67 (1H, ABd, *J* 6.8, OCH_B), 6.82–6.86 (2H, m, C(3′)*H*, C(5′)*H*), 7.14–7.17 (2H, m, C(2′)*H*, C(6′)*H*), 9.46 (1H, d, *J* 4.0, C(1)*H*); *m*/*z* (ESI^+) 328 ($[M+MeOH+H]^+$, 100%); HRMS (ESI^+) $C_{17}H_{30}NO_5^+$ ($[M+MeOH+H]^+$) requires 328.2118; found 328.2106.

Step 2: BuLi (2.5 M, 10.2 mL, 25.5 mmol) was added dropwise to a stirred solution of 4-methoxybenzyl triphenylphosphonium chloride[31] (12.3 g, 29.4 mmol) in THF (150 mL) at −78 °C. After 30 min, a solution of **72** (1.67 g) in THF (50 mL) at −78 °C was added. The reaction mixture was then allowed to warm to rt and stirred for 12 h. Satd aq NH_4Cl (20 mL) was then added and the resultant mixture was partitioned between brine (150 mL) and Et_2O (150 mL). The aqueous layer was then extracted with Et_2O (2×150 mL) and the combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 2:1) gave **74** as a colourless oil (223 mg, 9%, >99:1 dr); $C_{24}H_{33}NO_4$ requires C, 72.15; H, 8.3; N, 3.5%; found C, 72.1; H, 8.2; N, 3.4%; $[\alpha]_D^{20}$ +105 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2956 (C–H), 1608 (C=C); δ_H (400 MHz, $CDCl_3$) 1.05 (3H, d, *J* 6.6, C(5)H_3), 1.27 (3H, d, *J* 6.9, C(α)*Me*), 1.99 (3H, s, N*Me*), 3.09 (1H, app quintet, *J* 6.8, C(4)*H*), 3.36 (3H, s, CH_2O*Me*), 3.59 (1H, q, *J* 6.9, C(α)*H*), 3.81 (3H, s, ArO*Me*), 3.90 (3H, s, ArO*Me*), 4.55 (1H, ABd, *J* 6.6, OCH_A), 4.61(1H, dd, *J* 9.8, 6.6, C(3)*H*), 4.74 (1H, ABd, *J* 6.6, OCH_B), 5.45 (1H, dd, *J* 12.0, 9.8, C(2)*H*), 6.60 (1H, d, *J* 12.0, C(1)*H*), 6.80–6.87 (4H, m, *Ar*), 7.18–7.22 (2H, m, *Ar*), 7.27–7.30 (2H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 10.1 (C(α)*Me*), 21.0 (*C*(5)), 34.0 (N*Me*), 55.2, 55.3 (ArO*Me*), 55.7 (CH_2O*Me*), 57.1 (*C*(4)), 61.6 (*C*(α)), 74.8 (*C*(3)), 93.9 (OCH_2), 113.4, 114.1, 126.2, 128.3, 130.8 (*Ar*), 131.1 (*C*(2)), 131.6 (*C*(1)), 138.4 (*Ar*), 158.2, 158.5 (*C*(4′), *C*(4″)); *m*/*z* (ESI^+) 400 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{24}H_{34}NO_4^+$ ($[M+H]^+$) requires 400.2482; found 400.2467. Further elution gave a 50:50 mixture of **73** and **74** (107 mg, 5%). Further elution gave **73** as a colourless oil (1.49 g, 57%, >99:1 dr); $C_{24}H_{33}NO_4$ requires C, 72.15; H, 8.3; N, 3.5%; found C, 72.3; H, 8.4; N, 3.7%; $[\alpha]_D^{20}$ +19.7 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2965

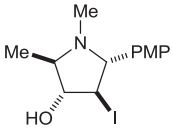
(C–H), 1609 (C=C); δ_H (400 MHz, $CDCl_3$) 1.11 (3H, d, *J* 6.6, C(5)H_3), 1.30 (3H, d, *J* 6.7, C(α)*Me*), 2.09 (3H, s, N*Me*), 3.13 (1H, dd, *J* 7.6, 6.6, C(4)*H*), 3.41 (3H, s, CH_2OMe), 3.66 (1H, q, *J* 6.7, C(α)*H*), 3.77 (3H, s, ArO*Me*), 3.84 (3H, s, ArO*Me*), 4.10 (1H, app t, *J* 8.2, C(3)*H*), 4.53 (1H, ABd, *J* 6.6, OCH_A), 4.79 (1H, ABd, *J* 6.6, OCH_B), 5.95 (1H, dd, *J* 16.0, 8.2, C(2)*H*), 6.43 (1H, d, *J* 16.0, C(1)*H*), 6.75–6.78 (2H, m, *Ar*), 6.88–6.91 (2H, m, *Ar*), 7.18–7.21 (2H, m, *Ar*), 7.33–7.36 (2H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 10.8 (C(α)*Me*), 21.0 (*C*(5)), 33.4 (N*Me*), 55.2, 55.3 (ArO*Me*), 55.7 (CH_2OMe), 57.0 (*C*(4)), 61.5 (*C*(α)), 79.8 (*C*(3)), 93.6 (OCH_2), 113.5, 114.0 (*Ar*), 126.9 (*C*(2)), 127.3, 128.3, 129.8 (*Ar*), 131.6 (*C*(1)), 138.3 (*Ar*), 158.2, 159.1 (*C*(4′), *C*(4″)); *m*/*z* (ESI^+) 400 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{24}H_{34}NO_4^+$ ($[M+H]^+$) requires 400.2482; found 400.2473.

4.28. (*R*,*R*,*R*,*R*)-*N*(1)-Methyl-2-(4′-methoxyphenyl)-3-iodo-4-*O*-methoxymethyl-5-methylpyrrolidine 75



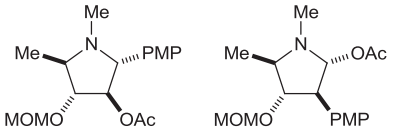
$NaHCO_3$ (941 mg, 11.2 mmol) and I_2 (2.85 g, 11.2 mmol) were added to a stirred solution of **73** (1.49 g, 3.73 mmol) in MeCN (50 mL) at −20 °C. After stirring for 2 h at −20 °C, the reaction mixture was allowed to warm to rt over 20 h then diluted with Et_2O (100 mL). The resultant mixture was washed with satd aq $Na_2S_2O_3$ (100 mL) then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 4:1) gave **75** as a colourless oil (790 mg, 54%, >99:1 dr); $C_{15}H_{22}INO_3$ requires C, 46.05; H, 5.7; N, 3.6%; found C, 46.2; H, 5.6; N, 3.5%; $[\alpha]_D^{20}$ +2.9 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2934 (C–H); δ_H (400 MHz, $CDCl_3$) 1.22 (3H, d, *J* 6.8, C(5)*Me*), 2.13 (3H, s, N*Me*), 3.43 (3H, s, CH_2OMe), 3.48–3.50 (1H, dq, *J* 6.8, 2.0, C(5)*H*), 3.83 (3H, s, ArO*Me*), 3.90 (1H, m, C(3)*H*), 3.93 (1H, m, C(2)*H*), 4.26 (1H, dd, *J* 3.7, 2.0, C(4)*H*), 4.74 (1H, ABd, *J* 6.8, OCH_A), 4.81 (1H, ABd, *J* 6.8, OCH_B), 6.87–6.91 (2H, m, C(3′)*H*, C(5′)*H*), 7.30–7.34 (2H, m, C(2′)*H*, C(6′)*H*); δ_C (100 MHz, $CDCl_3$) 12.3 (C(5)*Me*), 34.4 (*C*(3)), 34.5 (N*Me*), 55.2, 55.7 (O*Me*), 64.2 (*C*(5)), 76.0 (*C*(2)), 90.9 (*C*(4)), 95.8 (OCH_2), 113.9 (*C*(3′), *C*(5′)), 129.0 (*C*(2′), *C*(6′)), 130.9 (*C*(1′)), 159.5 (*C*(4′)); *m*/*z* (ESI^+) 392 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{15}H_{23}INO_3^+$ ($[M+H]^+$) requires 392.0717; found 392.0703.

4.29. (*R*,*R*,*R*,*R*)-*N*(1)-Methyl-2-(4′-methoxyphenyl)-3-iodo-4-hydroxy-5-methylpyrrolidine hydrochloride 76·HCl



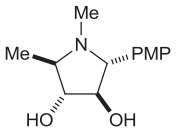
HCl (2 M in MeOH, 0.10 mL, 0.20 mmol) was added to a stirred solution of **75** (34 mg, 0.09 mmol) in MeOH (2 mL) and the resultant mixture was stirred at rt for 48 h to give **76**·HCl (16 mg, 52%, >99:1 dr); $[\alpha]_D^{20}$ −1.4 (*c* 0.5 in $CHCl_3$); ν_{max} (film) 2965 (C–H); δ_H (400 MHz, CD_3OD) [selected peaks] 1.54 (3H, d, *J* 6.8, C(5)*Me*), 2.49 (3H, br s, N*Me*), 3.66–3.72 (1H, br s, O*H*), 3.86 (3H, s, ArO*Me*), 7.05–7.08 (2H, m, C(3′)*H*, C(5′)*H*), 7.43–7.46 (2H, m, C(2′)*H*, C(6′)*H*); *m*/*z* (ESI^+) 348 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{13}H_{19}INO_2^+$ ($[M+H]^+$) requires 348.0455; found 348.0444.

4.30. (*R*,*R*,*R*,*R*)-*N*(1)-Methyl-2-(4′-methoxyphenyl)-3-acetoxy-4-*O*-methoxymethyl-5-methylpyrrolidine 78 and (*R*,*R*,*R*,*R*)-*N*(1)-methyl-2-acetoxy-3-(4′-methoxyphenyl)-4-*O*-methoxymethyl-5-methylpyrrolidine 79



AgOAc (641 mg, 3.84 mmol) was added to a stirred solution of **75** (500 mg, 1.28 mmol) in AcOH (10 mL) and the resultant mixture was heated at 40 °C for 24 h, then allowed to cool to rt. The mixture was then partitioned between satd aq $NaHCO_3$ (50 mL) and CH_2Cl_2 (50 mL) and the organic layer was dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 1:1) gave a 75:25 mixture of **78** and **79** as a colourless oil (199 mg, 48%, >99:1 dr). Data for **78**: δ_H (400 MHz, $CHCl_3$) 1.15 (3H, d, *J* 6.8, C(5)*Me*), 2.05 (3H, s, CO*Me*), 2.11 (3H, s, N*Me*), 3.27 (1H, app qd, *J* 6.8, 2.7, C(5)*H*), 3.40 (3H, s, CH_2OMe), 3.72 (1H, d, *J* 4.0, C(2)*H*), 3.81 (3H, s, ArO*Me*), 3.81 (1H, dd, *J* 2.7, 1.8, C(4)*H*), 4.70 (1H, ABd, *J* 6.6, OCH_A), 4.88 (1H, ABd, *J* 6.6, OCH_B), 5.06–5.09 (1H, m, C(3)*H*), 6.84–6.88 (2H, m, C(3′)*H*, C(5′)*H*), 7.24–7.28 (2H, m, C(2′)*H*, C(6′)*H*); δ_C (100 MHz, $CDCl_3$) 12.5 (C(5)*Me*), 21.1 (CO*Me*), 34.8 (N*Me*), 55.2, 55.6 (O*Me*), 63.2 (*C*(5)), 71.7 (*C*(2)), 85.0 (*C*(3)), 85.8 (*C*(4)), 95.4 (OCH_2O), 113.7 (*C*(3′), *C*(5′)), 129.6 (*C*(2′), *C*(6′)), 131.2 (*C*(1′)), 159.1 (*C*(4′)), 170.1 (*C*OMe). Data for **79**: δ_H (400 MHz, $CHCl_3$) 1.15 (3H, d, *J* 6.8, C(5)*Me*), 2.02 (3H, s, CO*Me*), 2.08 (3H, s, N*Me*), 2.72 (1H, m, C(5)*H*), 3.04 (1H, m, C(3)*H*), 3.34 (3H, s, CH_2OMe), 3.62 (1H, m, C(4)*H*), 3.80 (3H, s, ArO*Me*), 4.53 (1H, ABd, *J* 6.5, OCH_A), 4.56 (1H, ABd, *J* 6.5, OCH_B), 5.74 (1H, d, *J* 6.8, C(2)*H*), 6.85–6.87 (2H, m, C(3′)*H*, C(5′)*H*), 7.33–7.36 (2H, m, C(2′)*H*, C(6′)*H*); δ_C (100 MHz, $CDCl_3$) 18.4 (C(5)*Me*), 21.3 (CO*Me*), 34.8 (N*Me*), 55.3, 55.6 (O*Me*), 68.2 (*C*(5)), 74.7 (*C*(2)), 75.9 (*C*(3)), 85.0 (*C*(4)), 95.3 (OCH_2O), 113.7 (*C*(3′), *C*(5′)), 128.8 (*C*(2′), *C*(6′)), 131.2 (*C*(1′)), 159.1 (*C*(4′)), 170.1 (*C*OMe). Data for mixture: *m*/*z* (ESI^+) 324 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{17}H_{26}NO_5^+$ ($[M+H]^+$) requires 324.1805; found 324.1794.

4.31. (*R*,*R*,*R*,*R*)-*N*(1)-Methyl-2-(4′-methoxyphenyl)-3-hydroxy-4-hydroxy-5-methylpyrrolidine [(−)-codonopsinine] 14



HCl (2 M in MeOH, 0.59 mL, 1.18 mmol) was added to a stirred solution of the 75:25 mixture of **78** and **79** (180 mg, 0.56 mmol) in MeOH (5 mL) and the resultant mixture was heated at 50 °C for 48 h. The mixture was then concentrated in vacuo and the residue was partitioned between satd aq $NaHCO_3$ (5 mL) and EtOAc (5 mL). The organic layer was then dried and concentrated in vacuo. Purification via flash column chromatography (eluent CH_2Cl_2/MeOH, 4:1) gave **14** as a white crystalline solid (61 mg, 30% from **75**, >99:1 dr);[4b] mp 147–150 °C; {lit.[15] mp 153–155 °C}; $[\alpha]_D^{20}$ −9.1 (*c* 0.1 in MeOH); {lit.[4a] $[\alpha]_D^{20}$ −8.8 (*c* 0.1 in MeOH)}; δ_H (400 MHz, pyridine-d_5) 1.34 (3H, d, *J* 6.8, C(5)*Me*), 2.23 (3H, s, N*Me*), 3.64 (3H, s, O*Me*), 3.67–3.72 (1H, m, C(5)*H*), 4.09 (1H, app d, *J* 6.8, C(2)*H*), 4.39 (1H, dd, *J* 4.4, 3.8, C(4)*H*), 4.65 (1H, dd, *J* 6.5, 4.4, C(3)*H*), 5.25 (2H, br

s, O*H*), 6.95 (2H, d, *J* 8.6, C(3′)*H*, C(5′)*H*), 7.31 (2H, d, *J* 8.6, C(2′)*H*, C(6′)*H*); δ_C (100 MHz, pyridine-d_5) 14.3 (C(5)*Me*), 35.2 (N*Me*), 55.5 (O*Me*), 65.7 (*C*(5)), 74.6 (*C*(2)), 85.6 (*C*(4)), 88.0 (*C*(3)), 114.7 (*C*(3′), *C*(5′)), 130.2 (*C*(2′), *C*(6′)), 135.4 (*C*(1′)), 160.1 (*C*(4′)); *m*/*z* (ESI$^+$) 238 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{20}NO_3^+$ ([M+H]$^+$) requires 238.1438; found 238.1437.

Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2012.03.045.

References and notes

1. (a) 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; (b) Davies, S. G.; Fletcher, A. M.; Hughes, D. G.; Lee, J. A.; Price, P. D.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E.; Williams, O. M. H. *Tetrahedron* **2011**, *67*, 9975.
2. (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*, 758.
3. Brock, E. A.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Thomson, J. E. *Org. Lett.* **2011**, *13*, 1594.
4. (a) Matkhalikova, C. F.; Malikov, V. M.; Yunusov, S. Y. *Khim. Prir. Soedin.* **1969**, *5*, 606; (b) Yagudaev, M. R.; Matkhalikova, S. F.; Malikov, V. M.; Yusunov, S. Y. *Khim. Prir. Soedin.* **1972**, 495.
5. Iida, H.; Yamazaki, N.; Kibayashi, C.; Nagase, H. *Tetrahedron Lett.* **1986**, *27*, 5393.
6. Toyao, A.; Tamura, O.; Takagi, H.; Ishibashi, H. *Synlett* **2003**, 35.
7. Chandrasekhar, S.; Jagadeshwar, V.; Prakash, S. J. *Tetrahedron Lett.* **2005**, *46*, 3127.
8. Chandrasekhar, S.; Saritha, B.; Jagadeshwar, V.; Prakash, S. J. *Tetrahedron: Asymmetry* **2006**, *17*, 1380.
9. Reddy, J. S.; Rao, B. V. *J. Org. Chem.* **2007**, *72*, 2224.
10. Wang, C. J.; Calabrese, J. C. *J. Org. Chem.* **1991**, *56*, 4341.
11. Haddad, M.; Larcheveque, M. *Synlett* **2003**, 274.
12. Yoda, H.; Nakajima, T.; Takabe, K. *Tetrahedron Lett.* **1996**, *37*, 5531.
13. Goti, A.; Cicchi, S.; Mannucci, V.; Cardona, F.; Guarna, F.; Merino, P.; Tejero, T. *Org. Lett.* **2003**, *5*, 4235.
14. Oliveira, D. F.; Severino, E. A.; Correia, C. R. D. *Tetrahedron Lett.* **1999**, *40*, 2083.
15. Severino, E. A.; Correia, C. R. D. *Org. Lett.* **2000**, *2*, 3039.
16. Kotland, A.; Accadbled, F.; Robeyns, K.; Behr, J. *J. Org. Chem.* **2011**, *76*, 4094.
17. Chowdhury, M. A.; Reissig, H.-U. *Synlett* **2006**, 2383.
18. Uraguchi, D.; Nakamura, S.; Ooi, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 7562.
19. For selected examples, see: (a) Bunnage, M. E.; Burke, A. J.; Davies, S. G.; Goodwin, C. J. *Tetrahedron: Asymmetry* **1995**, *6*, 165; (b) Bunnage, M. E.; Burke, A. J.; Davies, S. G.; Millican, N. L.; Nicholson, R. L.; Roberts, P. M.; Smith, A. D. *Org. Biomol. Chem.* **2003**, *1*, 3708; (c) 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; (d) Abraham, E.; Davies, S. G.; Millican, N. L.; Nicholson, R. L.; Roberts, P. M.; Smith, A. D. *Org. Biomol. Chem.* **2008**, *6*, 1655; (e) 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.
20. For a review, see: Davies, S. G.; Smith, A. D.; Price, P. D. *Tetrahedron: Asymmetry* **2005**, *16*, 2833.
21. (a) Davis, F. A.; Towson, J. C.; Weismiller, M. C.; Lal, G. S.; Carroll, P. J. *J. Am. Chem. Soc.* **1988**, *110*, 8477; (b) Towson, J. C.; Weismiller, M. C.; Lal, G. S.; Sheppard, A. C.; Kumar, A.; Davis, F. A. *Org. Synth.* **1990**, *69*, 158; (c) Chen, B.-C.; Murphy, C. K.; Kumar, A.; Reddy, R. T.; Clark, C.; Zhou, P.; Lewis, B. M.; Gala, D.; Mergelsberg, I.; Scherer, D.; Buckley, J.; DiBenedetto, D.; Davis, F. A. *Org. Synth.* **1996**, *73*, 159.
22. Davies, S. G.; Lee, J. A.; Roberts, P. M.; Thomson, J. E.; West, C. J. *Tetrahedron Lett.* **2011**, *52*, 6477.
23. Crystallographic data (excluding structure factors) for compounds **14**, **25**, **27**, **42**, **45**·HCl and **76**·HCl have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 840036, 843707, 843708, 843709, 843710 and 840035, respectively. 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.
24. Flack, H. D. *Acta Crystallogr., Sect. A* **1983**, *39*, 876.
25. Flack, H. D.; Bernardinelli, G. *J. Appl. Crystallogr.* **2000**, *33*, 1143.
26. A 50:50 mixture of **73** and **74** was also isolated in 5% combined yield.
27. Ref. 6: $[\alpha]_D^{28}$ −13.2 (*c* 0.3 in MeOH); Ref. 7: $[\alpha]_D^{20}$ −8.8 (*c* 0.1 in MeOH); Ref. 8: $[\alpha]_D^{25}$ −12.4 (*c* 0.4 in MeOH); Ref. 9: $[\alpha]_D^{34}$ −8.7 (*c* 0.3 in MeOH); Ref. 11: $[\alpha]_D^{20}$ −10.5 (*c* 1.1 in MeOH); Ref. 13: $[\alpha]_D^{20}$ −7.2 (*c* 0.1 in MeOH); Ref. 15: mp 153–155 °C; $[\alpha]_D^{20}$ −7.3 (*c* 0.2 in MeOH); Ref. 18: $[\alpha]_D^{25}$ −13.1 (*c* 1.3 in MeOH).
28. Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.
29. Nakagawa, M.; Kawate, T.; Kakikawa, T.; Yamada, H.; Matsui, T.; Hino, T. *Tetrahedron* **1993**, *49*, 1739.
30. Blacker, A. J.; Brown, J. M.; Knight, F. I.; Lazzari, D.; Ricci, A. *Tetrahedron* **1997**, *53*, 11411.
31. Ketcham, R.; Jambotkar, D.; Martinelli, L. *J. Org. Chem.* **1962**, *47*, 4666.
32. A peak corresponding to *C*(1′) was not observed in the ^{13}C NMR spectrum of this compound.