Orthogonal *N*,*N*-deprotection strategies of β-amino esters

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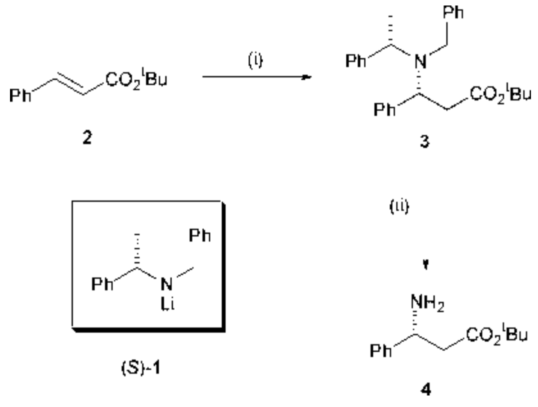
β-Amino esters derived from the stereoselective conjugate addition of homochiral lithium *N*-benzyl-*N*-α-methyl-4-methoxybenzylamide to α,β-unsaturated esters may be orthogonally mono-*N*-deprotected under either oxidative or acid-promoted reaction conditions. Further oxidative deprotection affords β-amino acids or β-lactams.

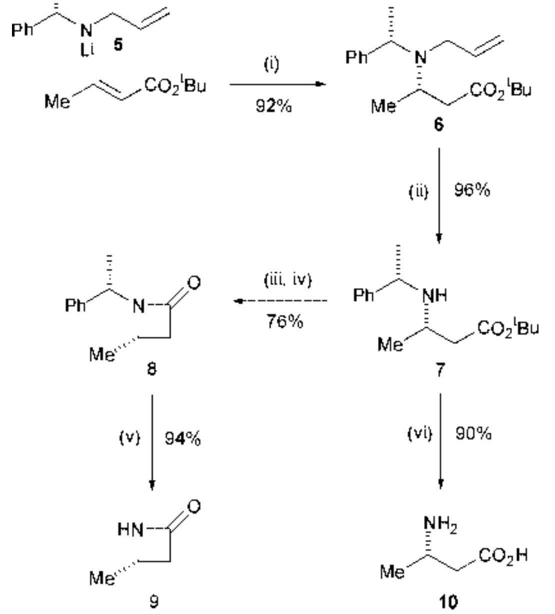
Introduction

β-Amino acids are an important class of natural product which are widespread among nature.[1] We have previously reported that a wide range of homochiral (enantiomerically pure) β-amino acid derivatives can be efficiently prepared *via* the conjugate addition of homochiral lithium amides derived from α-methylbenzylamine to α,β-unsaturated esters, and subsequent *N*-deprotection.[2] For example, addition of lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide **1** to *tert*-butyl cinnamate **2** affords *tert*-butyl (3*R*,α*S*)-3-(*N*-benzyl-*N*-α-methylbenzylamino)-3-phenylpropanoate **3** in >95% de, which on hydrogenolytic deprotection affords homochiral *tert*-butyl (*R*)-3-amino-3-phenylpropanoate **4** (Scheme 1).[3]



Scheme 1 *Reagents and conditions*: (*i*) (*S*)-**1** (1.6 equiv.), THF, −78 °C; (*ii*) Pd(OH)$_2$–C, MeOH, 5 atm H$_2$.

We have also described the extension of this methodology to the asymmetric synthesis of β-lactams, a distinct class of natural product displaying antimicrobial activity.[4] Thus, conjugate addition of lithium (*S*)-*N*-allyl-*N*-α-methylbenzylamide **5** to *tert*-butyl crotonate proceeds to give *tert*-butyl (3*S*,α*S*)-3-(*N*-allyl-*N*-α-methylbenzylamino)butanoate **6** in >95% de. Subsequent mono-deprotection of the tertiary amino functionality of β-amino ester **6** *via* treatment with Wilkinson's catalyst or *via* palladium-mediated deallylation affords *tert*-butyl (3*S*,α*S*)-3-(*N*-α-methylbenzylamino)butanoate **7**. Subsequent cyclisation to the β-lactam **8** and reductive deprotection of the *N*-α-methylbenzyl protecting group under Birch conditions affords β-lactam **9**. Alternatively, hydrogenation and ester hydrolysis of β-amino ester **7** yields the parent β-amino acid **10** (Scheme 2).[5]



Scheme 2 *Reagents and conditions*: (*i*) (*S*)-**5**, −78 °C, THF then NH$_4$Cl$_{(aq)}$; (*ii*) RhCl(PPh$_3$)$_3$, MeCN–H$_2$O (9 : 1), Δ; (*iii*) MeOH, HCl, RT; (*iv*) MeMgBr (1.1 equiv.), Et$_2$O, 0 °C; (*v*) Na–NH$_3$; (*vi*) Pd(OH)$_2$–C, 5 atm H$_2$, MeOH then H$^+$ and ion exchange.

While these approaches offer versatile routes to β-amino acid derivatives and homochiral templates for further manipulation, there are certain limitations regarding the functionality that may be incorporated into the target molecule due to the hydrogenolytic or Birch reduction conditions which are required for the direct removal of either the *N*-benzyl or the *N*-α-methylbenzyl protecting groups. We have previously reported that ceric ammonium nitrate (CAN) may be employed for the oxidative mono-debenzylation of *N*-benzyl tertiary amines,[6] and now report herein that this methodology may be employed as part of an orthogonal deprotection strategy for conjugate addition products derived from the stereoselective conjugate addition of a third generation lithium amide to α,β-unsaturated esters. Part of this work has been communicated previously.[7]

Results and discussion

Orthogonal deprotection strategies

The susceptibility of *N*-4-methoxybenzylamine protecting groups to undergo either oxidative[8] or acid promoted[9] benzylic cleavage under mild conditions prompted us to consider the use of commercially available (*S*)-*N*-α-methyl-4-methoxybenzyl-

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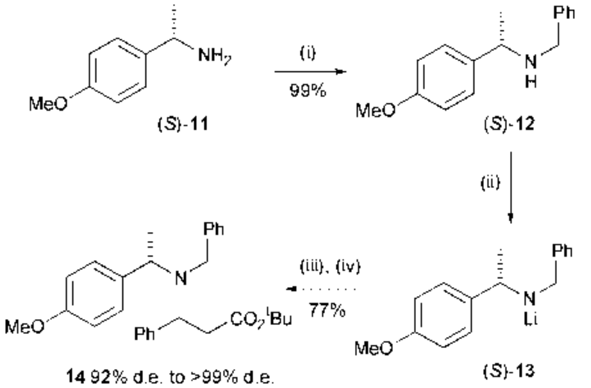
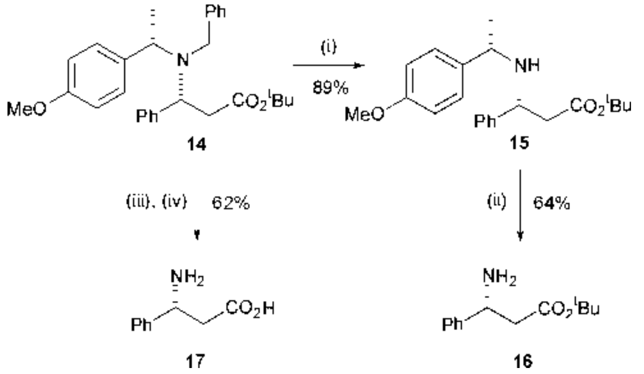
amine[10] **11** as the stereodirecting fragment of a homochiral ammonia equivalent. Thus, (*S*)-*N*-benzyl-*N*-α-methyl-4-methoxybenzylamine **12** was prepared *via* reductive amination of (*S*)-**11** with benzaldehyde. The capacity of homochiral lithium amide (*S*)-**13** to undergo stereoselective conjugate additions to α,β-unsaturated acceptors was initially investigated for the asymmetric synthesis of the known β-amino ester *tert*-butyl (*R*)-3-amino-3-phenylpropanoate **16**. Thus, deprotonation of (*S*)-**12** with *n*-BuLi in THF at −78 °C afforded lithium amide (*S*)-**13** which added to *tert*-butyl cinnamate to give *tert*-butyl (3*R*,α*S*)-3-(*N*-benzyl-*N*-α-methyl-4-methoxybenzylamino)-3-phenylpropanoate **14** in 92% crude de by ^{1}H NMR spectroscopy. Purification *via* chromatography on silica gel, followed by fractional recrystallisation (Et_2O–hexane 3 : 1) gave homochiral (3*R*,α*S*)-**14** in 77% yield as a single diastereoisomer (>99% de) by ^{1}H NMR spectroscopy (Scheme 3).



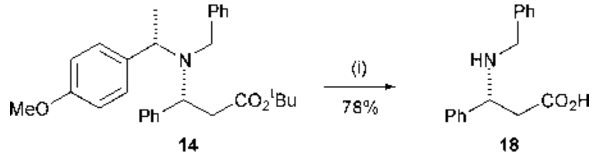
Scheme 3 *Reagents and conditions*: (*i*) benzaldehyde (1.05 equiv.), EtOH, Δ then $NaBH_4$, 0 °C to RT; (*ii*) *n*-BuLi, THF, −78 °C; (*iii*) *tert*-butyl cinnamate, THF, −78 °C; (*iv*) chromatography then recrystallisation [ether–hexane (3 : 1)].

Treatment of β-amino ester **14** with aqueous CAN (2.1 equiv.) resulted in mono-deprotection of the *N*-benzyl protecting group to afford *tert*-butyl (3*R*,α*S*)-3-(*N*-α-methyl-4-methoxybenzylamino)-3-phenylpropanoate **15** in 89% yield. Further treatment of (3*R*,α*S*)-**15** with aqueous CAN (4.0 equiv.) resulted in removal of the *N*-α-methyl-4-methoxybenzyl protecting group to afford *tert*-butyl (*R*)-3-amino-3-phenylpropanoate **16** in 64% yield {$[\alpha]_D^{23}$ +19.7 (*c* 0.96, $CHCl_3$); lit.[11] $[\alpha]_D^{23}$ *ent*-**16** −21.0 (*c* 1.0, $CHCl_3$)}. The susceptibility of both the *N*-benzyl and *N*-α-methyl-4-methoxybenzyl protecting groups to oxidative removal upon treatment with aqueous CAN suggested that the oxidative deprotection of these *N*-protecting groups could be achieved in a single step.[12] Therefore, treatment of (3*R*,α*S*)-**14** with CAN (6.0 equiv.) gave a crude reaction product[13] which, after acidic hydrolysis and purification by ion exchange chromatography, furnished (*R*)-3-amino-3-phenylpropionic acid **17** {$[\alpha]_D^{23}$ +6.8 (*c* 1.0, H_2O); lit.[14] $[\alpha]_D^{23}$ +6.5 (*c* 1.0, H_2O)} in 62% yield (Scheme 4).

Complementary methodology for the mono-deprotection of *N*-benzyl-*N*-α-methyl-4-methoxybenzyl protected β-amino ester **14** was also developed which relied upon the acid lability of the *N*-α-methyl-4-methoxybenzyl group. Thus, tertiary β-amino ester (3*R*,α*S*)-**14** in dichloromethane (DCM) was treated with TFA at RT, which resulted in deprotection of both the *tert*-butyl ester and *N*-α-methyl-4-methoxybenzyl protecting groups, to afford (*R*)-3-*N*-benzylamino-3-phenylpropionic acid **18** in 78% yield (Scheme 5).

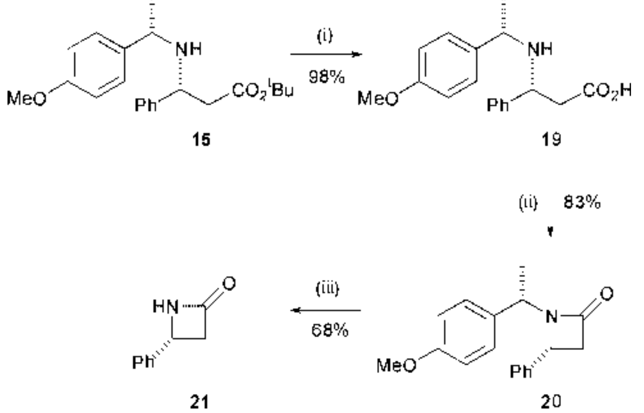


Scheme 4 *Reagents and conditions*: (*i*) CAN (2.1 equiv.), $MeCN–H_2O$ (5 : 1), RT; (*ii*) CAN (4.0 equiv.), $MeCN–H_2O$ (5 : 1), RT; (*iii*) CAN (6.0 equiv.), $MeCN–H_2O$ (5 : 1), RT; (*iv*) 1 M $HCl_{(aq)}$, Et_2O (1 : 1), RT then ion exchange chromatography.



Scheme 5 *Reagents and conditions*: (*i*) TFA–DCM (1 : 1), RT.

With selective complementary routes toward the *N*-α-methyl-4-methoxybenzyl protected β-amino ester **15** and *N*-benzyl protected β-amino ester **18** in hand, we investigated their conversion to their corresponding *N*-protected β-lactams. Thus, treatment of secondary amine (3*R*,α*S*)-**15** with TFA afforded (3*R*,α*S*)-3-(*N*-α-methyl-4-methoxybenzylamino)-3-phenylpropionic acid **19** in 96% yield. Subsequent ring closure with PPh_3–$(PyS)_2$ in refluxing acetonitrile[15] gave (4*R*,α*S*)-*N*-(α-methyl-4-methoxybenzyl)-4-phenylazetidin-2-one **20** in 83% yield. Oxidative removal of the *N*-α-methyl-4-methoxybenzyl protecting group from β-lactam **20** with aqueous CAN (3.0 equiv.) furnished (*R*)-4-phenylazetidin-2-one **21** in 68% yield (Scheme 6).[16] The stereochemical integrity of **21** was assumed to remain intact during this debenzylation on the basis of its specific rotation {$[\alpha]_D^{23}$ +136.9 (*c* 0.69, MeOH); lit.[17] $[\alpha]_D^{23}$ +132.0 (*c* 1.0, MeOH)}.

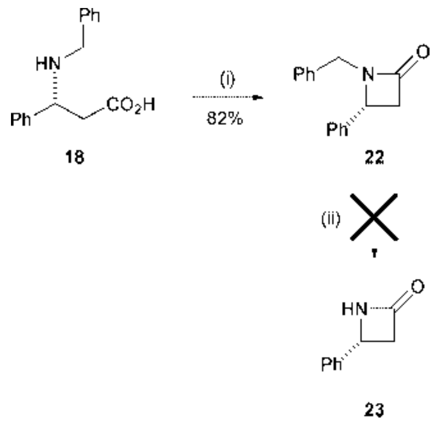


Scheme 6 *Reagents and conditions*: (*i*) TFA–DCM (1 : 2), RT; (*ii*) $(PyS)_2$ (1.2 equiv.), PPh_3 (1.2 equiv.), MeCN, Δ; (*iii*) CAN (3.0 equiv.), $MeCN–H_2O$ (5 : 1), RT.

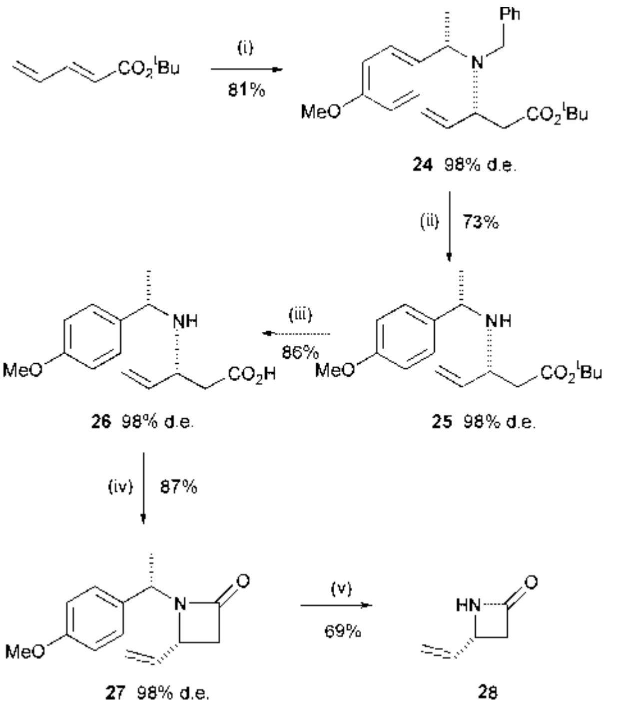
Alternatively, treatment of (*R*)-**18** with PPh_3–$(PyS)_2$ in refluxing acetonitrile gave (*R*)-*N*-benzyl-4-phenylazetidin-2-one **22**[18] in 82% yield. While *N*-benzyl β-lactams have been shown to be prone to debenzylation under Birch reduction conditions,[19] attempted CAN-promoted debenzylation to give the parent azetidin-2-one **23** returned only starting material. While we had anticipated that the β-lactam functionality might facilitate *N*-benzyl deprotection with CAN, this observation is consistent with previous reports by ourselves[6] and others[20] that cyclic tertiary *N*-benzylamines and *N*-benzylamides are inert to this oxidative protocol (Scheme 7).

Asymmetric synthesis of (*R*)-4-vinylazetidin-2-one

Unsaturated β-amino acid derivatives[21] have been shown to exhibit a range of biological activity and are sensitive to



Scheme 7 *Reagents and conditions*: (*i*) $(PyS)_2$ (1.2 equiv.), PPh_3 (1.2 equiv.), MeCN, Δ; (*ii*) CAN (3 equiv.), $MeCN–H_2O$ (5 : 1), RT.



Scheme 8 *Reagents and conditions*: (*i*) (*S*)-**13** (1.6 equiv.), THF, −78 °C; (*ii*) CAN (2.1 equiv.), $MeCN–H_2O$ (5 : 1), RT; (*iii*) TFA–DCM (1 : 2), RT; (iv) $(PyS)_2$ (1.2 equiv.), PPh_3 (1.2 equiv.), MeCN, Δ; (v) CAN (3.0 equiv.), $MeCN–H_2O$ (5 : 1), RT.

hydrogenation. Since the use of (*S*)-*N*-benzyl-*N*-α-methylbenzylamide **1** requires removal of the *N*-α-methylbenzyl protecting group from its conjugate addition products *via* hydrogenation, this amide cannot be readily used for the synthesis of such unsaturated β-amino acid derivatives.[22] The *N*-deprotection strategies developed herein for conjugate addition products of lithium amide (*S*)-**13** provides a route to this class of compound. This methodology was therefore applied toward the asymmetric synthesis of vinyl β-lactam **28**, an analogue of which has previously been used in the asymmetric synthesis of thienamycin precursors.[23] Thus, conjugate addition of lithium amide (*S*)-**13** to *tert*-butyl penta-2,4-dienoate gave *tert*-butyl (3*R*,α*S*)-3-(*N*-benzyl-*N*-α-methyl-4-methoxybenzylamino)pent-4-enoate **24** in 98% crude de by ^{1}H NMR, and in 81% yield and in 98% de after purification. Subsequent *N*-debenzylation with CAN gave *tert*-butyl (3*R*,α*S*)-3-(*N*-α-methyl-4-methoxybenzylamino)pent-4-enoate **25** in 73% yield and 98% de. Transformation of secondary amine **25** to its *N*-protected β-lactam derivative **27** *via* ester hydrolysis to afford the *N*-protected β-amino acid **26** (98% de) and cyclisation with $PPh_3–(PyS)_2$ gave (4*R*,α*S*)-**27** (98% de) in good yield. Treatment of **27** with CAN successfully cleaved the *N*-α-methyl-4-methoxybenzyl protecting group to afford the target β-lactam **28** in 69% yield with the vinylic functionality intact (Scheme 8).

Conclusions

Tertiary β-amino esters derived from conjugate addition of homochiral lithium *N*-benzyl-*N*-α-methyl-4-methoxybenzylamide **13** to α,β-unsaturated acceptors may be selectively mono-deprotected *via* treatment with CAN to afford *N*-4-methoxy-α-methylbenzyl β-amino esters. Subsequent cyclisation and oxidative deprotection of these adducts enables β-lactams to be obtained in good yield. Further applications of these deprotection strategies will be reported in due course.

Experimental

General experimental

All reactions involving organometallic or other moisture-sensitive reagents were performed under an atmosphere of nitrogen *via* standard vacuum line techniques. All glassware was flame-dried and allowed to cool under vacuum. THF was distilled under an atmosphere of dry nitrogen from sodium benzophenone ketyl. Water was distilled. *n*-Butyllithium was used as a solution in hexanes at the molarity stated. Ceric ammonium nitrate (ACS grade) was used as supplied. All other solvents and reagents were used as supplied (Analytical or HPLC grade), without prior purification. Reactions were dried with $MgSO_4$. Thin layer chromatography (TLC) was performed on aluminium sheets coated with 60 F_{254} silica gel. Sheets were visualised using iodine, UV light or 1% aqueous $KMnO_4$ solution. Flash chromatography was performed on Kieselgel 60 silica gel. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker DPX 400 (^{1}H: 400 MHz and ^{13}C: 100.6 MHz) or where stated on a Bruker AMX 500 (^{1}H: 500 MHz and ^{13}C: 125.3 MHz) spectrometer in the deuteriated solvent stated. All chemical shifts (δ) are quoted in ppm and coupling constants (J) in Hz. Coupling constants are quoted twice, each being recorded as observed in the spectrum without averaging. Residual signals from the solvents were used as an internal reference. ^{13}C multiplicities were assigned using a DEPT sequence. In all cases, the reaction diastereoselectivity was assessed by peak integration of the ^{1}H NMR spectrum of the crude reaction mixture. Infrared spectra were recorded on a Perkin–Elmer 1750 IR Fourier Transform spectrophotometer using either thin films on NaCl plates (film) or KBr discs (KBr) as stated. Only the characteristic peaks are quoted. Low resolution mass spectra (*m*/*z*) were recorded on a VG MassLab 20-250 or Micromass Platform 1 spectrometer and high resolution mass spectra (HRMS) on a Micromass Autospec 500 OAT spectrometer or on a Waters 2790 Micromass LCT Exact Mass Electrospray Ionisation Mass Spectrometer. Techniques used were chemical ionisation (CI, NH_3), atmospheric pressure chemical ionisation (APCI) or electrospray ionisation (ESI) using partial purification by HPLC with methanol–acetonitrile–water (40 : 40 : 20) as the eluent. Specific optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a water-jacketed 10 cm cell and are given in units of 10^{-1} deg cm^2 g^{-1}. Concentrations are quoted in g/100 ml. Melting points were recorded on a Leica VMTG Galen III apparatus and are uncorrected. Elemental analysis of crystalline **14** was performed by the microanalysis service of the Inorganic Chemistry Laboratory, Oxford; all other products were not amenable to analysis and so were characterised by high resolution mass spectrometry.

Representative procedure 1

n-Butyllithium (1.55 equiv.) was added dropwise to a stirred solution of *N*-benzyl-*N*-α-methyl-4-methoxybenzylamine **12**

(1.6 equiv.) in anhydrous THF at −78 °C under nitrogen. After thirty minutes, a solution of the α,β-unsaturated ester (1.0 equiv.) in anhydrous THF was added dropwise *via* cannula and the reaction was stirred at −78 °C for two hours before the addition of saturated aqueous ammonium chloride, and warmed to RT. The resultant solution was partitioned between brine and 1 : 1 DCM–Et$_2$O and the combined organic extracts dried (MgSO$_4$), filtered and concentrated *in vacuo* before purification by column chromatography.

Representative procedure 2

CAN was added portionwise to a stirred solution of the substrate (1.0 equiv.) in MeCN–H$_2$O (5 : 1) and stirred at RT. After sixteen hours, the reaction was quenched by the addition of saturated aqueous sodium bicarbonate solution and stirred vigorously for ten minutes before extraction with Et$_2$O. The combined organic extracts were dried (MgSO$_4$), filtered and concentrated *in vacuo* before purification by column chromatography.

Representative procedure 3

TFA was added dropwise to a stirred solution of the substrate in DCM and stirred at RT overnight. After concentration *in vacuo*, the residue was partitioned between saturated aqueous sodium bicarbonate solution (10 ml) and EtOAc (50 ml). The separated aqueous phase was extracted with EtOAc (5 × 50 ml), and the combined organic extracts dried (MgSO$_4$), filtered and concentrated *in vacuo* before purification by column chromatography.

Representative procedure 4

(PyS)$_2$ (1.2 equiv.) was added to a stirred solution of the substrate (1.0 equiv.) and PPh$_3$ (1.2 equiv.) in MeCN and heated at reflux overnight. After cooling, the reaction was concentrated *in vacuo* and the residue purified by column chromatography.

Preparation of (*S*)-*N*-benzyl-*N*-α-methyl-4-methoxybenzylamine 12

Benzaldehyde (7.0 ml, 69.3 mmol) was added dropwise to a stirred solution of (*S*)-*N*-α-methyl-4-methoxybenzylamine **11** (10.0 g, 66 mmol) in EtOH (150 ml) and heated at reflux. After two hours, the reaction was cooled to 0 °C before the portionwise addition of NaBH$_4$ (4.0 g, 105.6 mmol), and left to stir overnight. After concentration *in vacuo*, the residue was partitioned between H$_2$O (50 ml) and DCM (3 × 100 ml), dried and concentrated *in vacuo* to give **12** (15.8 g, 99%) as a colourless oil which was subsequently used without further purification; ν_{max}/cm^{-1} (film) 3320 (NH), 2959, 2832 (C–H), 1510, 1451 (OMe), 1243 (Ph–OMe); $[\alpha]^{19}_{D}$ −64.0 (*c* 1.0, CHCl$_3$); δ_H(400 MHz, CDCl$_3$) 1.36 [3H, d, *J* 6.6, C(α)*Me*], 3.70 (2H, ABq, NC*H*$_2$Ph), 3.78 [1H, q, *J* 6.6, C(α)*H*], 3.82 (3H, s, O*Me*), 6.90 [2H, m, Ph(3)*H* and Ph(5)*H* C$_6$H$_4$OMe], 7.24–7.37 [7H, m, Ph(2)*H* and Ph(6)*H* C$_6$H$_4$OMe; Ph]; δ_C (50 MHz, CDCl$_3$) 24.5, 51.6, 55.3, 56.9, 113.9, 126.9, 127.3, 127.8, 128.2, 128.4, 137.6, 140.7, 158.7; *m*/*z* APCI$^+$ 242.1 (MH$^+$, 10%), 264.2 (MNa$^+$, 5%), 134.9 (C$_9$H$_{11}$O$^+$, 100%); HRMS (CI$^+$) C$_{16}$H$_{20}$NO requires 242.1545; found 242.1548. The ee of this material was shown to be >99% by ^{1}H NMR chiral shift experiments with (*S*)-*O*-acetylmandelic acid and in comparison with a racemic sample.[24]

Preparation of *tert*-butyl (3*R*,α*S*)-3-(*N*-benzyl-*N*-α-methyl-4-methoxybenzylamino)-3-phenylpropanoate 14

Following representative procedure 1, *n*-butyllithium (1.6 M, 6.7 ml, 10.8 mmol), (*S*)-**12** (2.68 g, 11.1 mmol) in THF (20 ml) at −78 °C and *tert*-butyl (*E*)-cinnamate (1.42 g, 6.94 mmol) in THF (20 ml) gave, after successive purification by chromatography (hexane–Et$_2$O 10 : 1) and recrystallisation (Et$_2$O–hexane 3 : 1), **14** (2.37 g, 77%) as white needles; mp 83–84 °C (Et$_2$O–hexane); Found: C, 77.75; H, 7.65; N, 3.1%; C$_{29}$H$_{35}$NO$_3$ requires C, 78.2; H, 7.9; N, 3.1%; $[\alpha]^{20}_{D}$ −14.2 (*c* 1.0, CHCl$_3$); ν_{max}/cm^{-1} 1727 (C=O), 1511 (OMe), 1248 (Ph–OMe); δ_H(400 MHz, CDCl$_3$) 1.28 [9H, s, OC(*Me*)$_3$], 1.31 [3H, d, *J* 6.9, C(α)*Me*], 2.53 [1H, dd, $J_{2A,2B}$ 14.5, $J_{2A,3}$ 10.0, C(2)H_A], 2.60 [1H, dd, $J_{2B,2A}$ 14.5, $J_{2B,3}$ 5.1, C(2)H_B], 3.68 (2H, ABq, NC*H*$_2$Ph), 3.83 (3H, s, O*Me*), 4.00 [1H, q, *J* 6.9, C(α)*H*], 4.45 [1H, dd, $J_{3,2A}$ 10.0, $J_{3,2B}$ 5.1, C(3)*H*], 6.91 [2H, m, Ph(3)*H*, Ph(5)*H* C$_6$H$_4$OMe], 7.20–7.40 (10H, m, *Ph*), 7.47 [2H, m, Ph(2)*H*, Ph(6)*H* C$_6$H$_4$OMe]; δ_C (100 MHz, CDCl$_3$) 16.3, 27.8, 38.8, 50.8, 55.2, 56.3, 59.7, 80.1, 113.4, 126.4, 127.1, 127.9, 128.1, 128.2, 128.9, 136.1, 141.9, 142.0, 158.4, 171.2; *m*/*z* (CI$^+$) 446.5 (MH$^+$, 20%), 135 (C$_9$H$_{11}$O$^+$, 80%); HRMS (CI$^+$) C$_{19}$H$_{23}$INO$_3$ requires 446.2695, found 446.2689.

Preparation of *tert*-butyl (3*R*,α*S*)-3-(*N*-α-methyl-4-methoxybenzylamino)-3-phenylpropanoate 15

Following representative procedure 2, CAN (3.88 g, 7.08 mmol) was added to **14** (1.50 g, 3.37 mmol) in MeCN–H$_2$O (5 : 1) (24 ml) at RT. After work-up, purification by column chromatography on silica gel [hexane–Et$_2$O (8 : 1)–1% NEt$_3$], gave **15** (1.06 g, 89%) as a colourless oil; $[\alpha]^{20}_{D}$ −21.7 (*c* 0.97, CHCl$_3$); ν_{max}/cm^{-1} (film) 3338 (br, NH), 2975, 2931 (C–H), 1725 (C=O), 1512 (OMe), 1246 (Ph–OMe), 1151 (C–O); δ_H(400 MHz, CDCl$_3$) 1.34 [3H, d, *J* 6.4, C(α)*Me*], 1.38 [9H, s, OC(*Me*)$_3$], 2.53 [1H, dd, $J_{2A,2B}$ 15.3, $J_{2A,3}$ 6.2, C(2)H_A], 2.61 [1H, dd, $J_{2A,2B}$ 15.3, $J_{2B,3}$ 7.9, C(2)H_B], 3.62 [1H, q, *J* 6.4, C(α)*H*], 3.79 (3H, s, O*Me*), 4.15 [1H, dd, $J_{2A,3}$ 6.2, $J_{2B,3}$ 7.9, C(3)*H*], 6.84 [2H, m, Ph(3), Ph(5) C$_6$H$_4$OMe], 7.19 [2H, d, *J* 8.2, Ph(2), Ph(6) C$_6$H$_4$OMe], 7.23–7.38 (5H, m, Ph); δ_C 22.2, 28.0, 43.9, 53.8, 55.2, 57.0, 80.4, 113.7, 127.1, 127.2, 127.6, 128.4, 138.2, 142.9, 158.4, 171.0; *m*/*z* APCI$^+$ 356.2 (MH$^+$, 10%), 134.9 (C$_9$H$_{11}$O$^+$, 100%); HRMS (CI$^+$) C$_{22}$H$_{29}$NO$_5$ requires 356.2232; found 356.2226.

Preparation of *tert*-butyl (*R*)-3-phenyl-3-aminopropanoate[11] 16

Following representative procedure 2, CAN (5.55 g, 10.1 mmol) was added to **15** (899 mg, 2.53 mmol) in 5 : 1 MeCN–H$_2$O (24 ml). After work-up, purification by column chromatography on silica gel (hexane–Et$_2$O 1 : 2) gave **16** (358 mg, 64%) as a yellow oil; $[\alpha]^{23}_{D}$ +19.7 (*c* 0.96, CHCl$_3$); lit.[11] $[\alpha]^{23}_{D}$ for *ent*-**16** −21.0 (*c* 1.0, CHCl$_3$); δ_H(400 MHz, CDCl$_3$) 1.42 [9H, s, OC(*Me*)$_3$], 1.79 (2H, br s, N*H*$_2$), 2.59 [2H, m, C(2)*H*$_2$], 4.38 [1H, app t, *J* 6.5, C(3)*H*], 7.24–7.37 (5H, m, Ph).

Preparation of (*R*)-3-phenyl-3-aminopropionic acid[14] 17

CAN (5.91 g, 10.8 mmol) was added to a stirred solution of **14** (800 mg, 1.79 mmol) in MeCN–H$_2$O (5 : 1) (36 ml) at RT. After sixteen hours, saturated aqueous sodium bicarbonate solution (10 ml) was added and the resultant solution extracted with Et$_2$O (3 × 100 ml), dried and concentrated *in vacuo* to yield a yellow oil which was dissolved in Et$_2$O (5 ml) before the dropwise addition of 1 M HCl$_{(aq)}$ (5 ml), and stirred at RT. After a further sixteen hours, the aqueous and organic layers were separated. The aqueous layer was concentrated *in vacuo* to yield a pale yellow solid which was purified by ion exchange chromatography using Dowex 50X8–200 to give **17** as a white solid (189 mg, 64%); $[\alpha]^{23}_{D}$ +6.8 (*c* 1.0, H$_2$O); lit.[14] $[\alpha]^{23}_{D}$ +6.5 (*c* 1.0, H$_2$O); δ_H(400 MHz, D$_2$O) 2.59 [2H, m, C(2)*H*$_2$], 4.38 [1H, app t, *J* 6.5, C(3)*H*], 7.24–7.37 (5H, m, Ph).

Preparation of (*R*)-3-*N*-benzylamino-3-phenylpropionic acid 18

Following representative procedure 3, TFA (4 ml) and **14** (1.0 g, 2.24 mmol) in DCM (4 ml) gave, after work-up and purification by column chromatography on silica gel (CHCl$_3$–MeOH 10 : 1), **18** (446 mg, 78%) as an off-white solid; $[\alpha]^{24}_{D}$ +56.3 (*c* 1.0, MeOH); ν_{max}/cm^{-1} (film) 3030 (C–H), 1560 (C=O); δ_H (400 MHz, $CDCl_3$) 2.62 [1H, dd, $J_{2A,2B}$ 17.1, $J_{2A,3}$ 1.9, C(2)H_A], 3.00 [1H, dd, $J_{2B,2A}$17.1, $J_{2B,3}$ 11.7, C(2)H_B], 3.57 (1H, d, *J* 13.6, NCH_A), 4.16 [1H, dd, $J_{3,2B}$ 11.7, $J_{3,2A}$ 1.9, C(3)*H*], 4.31 (1H, d, *J* 13.6, NCH_A), 7.29–7.47 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 40.4, 47.4, 57.9, 128.0, 128.7, 128.8, 128.9, 129.3, 129.4, 130.6, 132.5, 135.8, 176.2; *m/z* APCI$^+$ 256.2 (MH$^+$, 100%); HRMS (CI$^+$) $C_{16}H_{18}NO_2$ requires 256.1338; found 256.1343.

Preparation of (3*R*,α*S*)-3-(*N*-α-methyl-4-methoxybenzylamino)-3-phenylpropionic acid 19

Following representative procedure 3, **15** (800 mg, 2.25 mmol) and TFA (5 ml) in DCM (6 ml) gave, after work-up and purification by column chromatography on silica gel ($CHCl_3$–MeOH 10 : 1), **19** (645 mg, 96%) as a white foam; $[a]_D^{24}$ +12.3 (*c* 1.0, MeOH); ν_{max}/cm^{-1} (film) 1642 (C=O), 1513 (OMe), 1203 (Ph–OMe); δ_H (400 MHz, $CDCl_3$) 1.67 [3H, d, *J* 6.5, C(α)*Me*], 2.67–2.80 [2H, m, C(2)H_2], 3.80 (3H, s, O*Me*), 4.12 [1H, q, *J* 6.4, C(α)*H*], 4.54–4.59 [1H, m, C(3)*H*], 6.94–6.98 [2H, m, Ph(3), Ph(5) C_6H_4OMe], 7.25–7.29 [2H, m, Ph(2), Ph(6) C_6H_4OMe], 7.43–7.52 (5H, m, *Ph*); δ_C(100 MHz, $CDCl_3$) 19.5, 40.3, 56.3, 56.7, 59.7, 1136.1, 129.3, 130.0, 130.9, 131.2, 137.2, 162.3, 177.8; *m/z* APCI$^+$ 300.2 (MH+, 15%), 134.9 ($C_9H_{11}O^+$, 100%); HRMS (CI$^+$) $C_{18}H_{22}NO_5$ requires 356.1599; found 356.1601.

Preparation of (4*R*,α*S*)-*N*-(α-methyl-4-methoxybenzyl)-4-phenylazetidin-2-one 20

Following representative procedure 4, $(PyS)_2$ (440 mg, 2.0 mmol), PPh_3 (524 mg, 2.0 mmol) and **19** (500 mg, 1.67 mmol) were heated in refluxing MeCN (50 ml). After work-up, the residue was purified by column chromatography on silica gel (hexane–Et_2O 1 : 1) to give **20** (391 mg, 83%) as a colourless oil; $[a]_D^{24}$ +45.1 (*c* 1.0, $CDCl_3$); ν_{max}/cm^{-1} (film) 3031, 2976 (C–H), 1746 (C=O), 1509 (OMe), 1245 (Ph–OMe); δ_H (400 MHz, $CDCl_3$) 1.26 [3H, d, *J* 7.5, C(α)*Me*], 2.81 [1H, dd, $J_{3A,3B}$ 14.5, $J_{3A,4}$ 2.2, C(3)H_A], 3.22 [1H, dd, $J_{3B,3A}$ 14.5, $J_{3A,4}$ 5.3, C(3)H_B], 3.81 (3H, s, O*Me*), 5.00 [1H, q, *J* 7.5, C(α)*H*], 4.25 (1H, dd, $J_{4,3B}$ 5.3, $J_{4,3A}$ 2.2), 6.83–6.87 [2H, m, Ph(3), Ph(5) C_6H_4OMe], 7.11–7.15 [2H, m, Ph(2), Ph(6) C_6H_4OMe], 7.27–7.37 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.9, 446.2, 0.3, 51.5, 53.1, 59.7, 113.1, 129.3, 130.0, 130.9, 131.2, 137.2, 162.3, 177.8; *m/z* APCI$^+$ 282.2 (MH$^+$, 100%); HRMS (CI$^+$) $C_{18}H_{20}NO_2$ requires 282.1494; found 282.1489.

Preparation of (*R*)-4-phenylazetidin-2-one[17] 21

Following representative procedure 2, CAN (592 mg, 1.08 mmol) and **20** (100 mg, 0.36 mmol) in MeCN–H_2O (5 : 1) gave, after work-up and purification by column chromatography on silica gel (hexane–Et_2O 1 : 1), **21** (36 mg, 68%) as a colourless oil; $[a]_D^{23}$ +136.9 (*c* 0.69, MeOH), $[a]_D^{23}$ lit.[17] +132.0 (*c* 1, MeOH); δ_H (400 MHz, $CDCl_3$) 2.88 [1H, ddd, $J_{3A,3B}$ 14.0, $J_{3A,4}$ 2.5, $J_{3A,NH}$ 1.0, C(3)H_A], 3.45 [1H, ddd, $J_{3B,3A}$ 14.0, $J_{3B,4}$ 5.3, $J_{3B,NH}$ 2.4, C(3)H_B], 4.73 [1H, dd, $J_{4,3B}$ 5.3, $J_{4,3A}$ 2.5, C(4)*H*], 6.30 (1H, br s, N*H*), 7.31–7.42 (5H, m, *Ph*).

Preparation of (*R*)-*N*-benzyl-4-phenylazetidin-2-one[18] 22

Following representative procedure 4, $(PyS)_2$ (311 mg, 1.2 mmol), PPh_3 (370 mg, 1.41 mmol) and **18** (300 mg, 1.18 mmol) were heated in refluxing MeCN (50 ml). After work-up, the residue was purified by column chromatography on silica gel (hexane–Et_2O 2 : 1) to give **22** (228 mg, 82%) as a colourless oil; $[a]_D^{23}$ +94.5 (*c* 1.0, MeOH), $[a]_D^{23}$ lit. (*ent*-**22**)[18] −54.4 (*c* 0.59, MeOH); δ_H (400 MHz, $CDCl_3$) 2.87 [1H, dd, $J_{3A,3B}$ 14.7, $J_{3A,4}$ 1.7, C(3)H_A], 3.35 [1H, dd, $J_{3B,3A}$ 14.7, $J_{3A,4}$ 5.5, C(3)H_B], 3.76 (1H, d, *J* 15.1, NCH_A), 4.40 [1H, dd, $J_{4,3B}$ 5.5, $J_{4,3A}$ 1.7, C(4)*H*], 4.81 (1H, d, *J* 15.1, NCH_B), 7.13–7.16 (2H, m, *Ph*), 7.25–7.39 (8H, m, *Ph*).

Preparation of *tert*-butyl (3*R*,α*S*)-3-(*N*-benzyl-*N*-α-methyl-4-methoxybenzylamino)pent-4-enoate 24

Following representative procedure 1, *n*-butyllithium (2.5 M, 6 ml, 15.1 mmol), (*S*)-**12** (3.75 g, 15.6 mmol) in THF (20 ml) at −78 °C and *tert*-butyl (*E*)-penta-2,4-dienoate (1.5 g, 9.73 mmol) in THF (30 ml) gave, after purification by chromatography (hexane–Et_2O 16 : 1), **24** (3.1 g, 81%) as a colourless oil; $[a]_D^{24}$ +8.7 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} (film) 2975 (C–H), 1726 (C=O), 1609 (C=C), 1509 (OMe), 1247 (Ph–OMe); δ_H(400 MHz, $CDCl_3$) 1.36 [3H, d, *J* 6.8, C(α)*Me*], 1.39 [9H, s, OC$(Me)_3$], 2.27 [1H, dd, $J_{2A,2B}$ 14.4, $J_{2A,3}$ 8.9, C(2)H_A], 2.34 [1H, dd, $J_{2B,2A}$ 14.4, $J_{2B,3}$ 5.3, C(2)H_B], 3.65 (2H, ABq, NCH_2Ph), 3.0 (3H, s, O*Me*), 3.81–3.88 [1H, m, C(3)H], 3.96 [1H, q, *J* 6.8, C(α)*H*], 5.10–5.27 [2H, m, C(5)H_2], 5.89–5.98 [1H, m, C(4)*H*], 6.84 [2H, m, Ph(3)*H*, Ph(5)*H* C_6H_4OMe], 7.19–7.35 (7H, m, *Ph*); δ_C(100 MHz, $CDCl_3$) 12.2, 18.1, 38.5, 50.3, 55.2, 56.9, 57.2, 80.1, 113.3, 115.8, 126.5, 128.1, 128.2, 128.8, 136.2, 138.7, 141.6, 158.3, 171.2; *m/z* (CI$^+$) 396.4 (MH$^+$, 20%), 135.1 ($C_9H_{11}O^+$, 100%); HRMS (CI$^+$) $C_{25}H_{34}NO_3$ requires 396.2539, found 396.2531.

Preparation of *tert*-butyl (3*R*,α*S*)-3-(*N*-α-methyl-4-methoxybenzylamino)pent-4-enoate 25

Following representative procedure 2, CAN (3.9 g, 7.1 mmol) was added to **24** (1.0 g, 2.54 mmol) in MeCN–H_2O (5 : 1) (30 ml) at RT. After work-up, purification by column chromatography on silica gel [hexane–Et_2O (5 : 1)–1% NEt_3] gave **25** (562 mg, 73%) as a colourless oil; $[a]_D^{24}$ −58.6 (*c* 1.05, $CHCl_3$); ν_{max}/cm^{-1} (film) 2973, 2835 (C–H), 1726 (C=O), 1609 (C=C), 1511 (OMe), 1243 (Ph–OMe), 1161 (C–O); δ_H(400 MHz, $CDCl_3$) 1.31 [3H, d, *J* 6.5, C(α)*Me*], 1.45 [9H, s, OC$(Me)_3$], 2.39–2.41 [2H, m, C(2)H_2], 3.49 [1H, m, C(3)*H*], 3.80 (3H, s, O*Me*), 3.81 [1H, q, *J* 6.4, C(α)*H*], 5.07–5.17 [2H, m, C(5)H_2], 5.62–5.70 [1H, m, C(4)*H*], 6.83–6.87 [2H, m, Ph(3)*H*, Ph(5)*H* C_6H_4OMe], 7.23–7.27 [2H, d, *J* 8.2, Ph(2)*H*, Ph(6)*H* C_6H_4OMe]; δ_C(100 MHz, $CDCl_3$) 23.0, 28.1, 41.3, 53.9, 55.2, 57.8, 80.5, 113.7, 115.6, 128.2, 138.1, 139.7, 158.5, 171.0; *m/z* APCI$^+$ 306.3 (MH$^+$, 15%), 135.1 ($C_9H_{11}O^+$, 100%); HRMS (ESI) $C_{18}H_{28}NO_5$ requires 306.2069; found 306.2068.

Preparation of (3*R*,α*S*)-3-(*N*-α-methyl-4-methoxybenzylamino)-pent-4-enoic acid 26

Following representative procedure 3, TFA (4 ml) and **25** (800 mg, 2.63 mmol) in DCM (10 ml) gave, after work-up and purification by column chromatography on silica gel ($CHCl_3$–MeOH 10 : 1), **26** (562 mg, 86%) as a white solid; $[a]_D^{23}$ +14.7 (*c* 1, MeOH); ν_{max} (film/cm^{-1}) 1612 (C=O), 1516 (OMe), 1252 (Ph–OMe); δ_H (500 MHz, d_4-MeOH) 1.86 [3H, d, *J* 6.9, C(α)*Me*], 2.68 [1H, dd, $J_{2A,2B}$ 16.7, $J_{2A,3}$ 8.5, C(2)H_A], 2.79 [1H, dd, $J_{2B,2A}$ 16.7, $J_{2B,3}$ 4.5, C(2)H_B], 4.04 (3H, s, O*Me*), 4.21–4.25 [1H, br m, C(3)*H*], 4.55 [1H, q, *J* 6.9, C(α)*H*], 5.66–5.74 [2H, m, C(5)H_2], 6.00–6.07 [1H, m, C(4)*H*], 7.22–7.25 [2H, m, Ph(3)*H* and Ph(5)*H* C_6H_4OMe], 7.60–7.63 [2H, m, Ph(2)*H* and Ph(6)*H* C_6H_4OMe]; δ_C (125 MHz, d_4-MeOH) 19.2, 36.7, 56.2, 56.3, 58.5, 116.2, 123.4, 130.0, 131.3, 133.8, 162.4, 177.6; *m/z* APCI$^+$ 250.2 (MH$^+$, 30%), 135.1 ($C_9H_{11}O^+$, 100%); HRMS (ESI) $C_{14}H_{19}NO_3Na$ requires 272.1263; found 272.1272.

Preparation of (4*R*,α*S*)-*N*-(α-methyl-4-methoxybenzyl)-4-vinylazetidin-2-one 27

Following representative procedure 4, $(PyS)_2$ (425 mg, 1.93 mmol), PPh_3 (505 mg, 1.93 mmol) and **26** (400 mg, 1.61 mmol) were heated in refluxing MeCN (80 ml). After cooling and concentration of the reaction *in vacuo*, column chromatography of the residue on silica gel (Et_2O–hexane 1 : 1) gave **27** (325 mg, 87%) as a colourless oil; $[a]_D^{24}$ −97.0 (*c* 1.05, $CHCl_3$); ν_{max}/cm^{-1} (film) 2976 (C–H), 1746 (C=O), 1513 (OMe), 1244 (Ph–OMe); δ_H(400 MHz, $CDCl_3$) 1.54 [3H, d, *J* 7.2, C(α)*Me*], 2.62 [1H, dd,

$J_{3A,3B}$ 14.6, $J_{3A,4}$ 1.7, C(3)H_A], 3.03 [1H, dd, $J_{3B,3A}$ 14.6, $J_{3B,4}$ 5.1, C(3)H_B], 3.79–3.83 [1H, m, C(4)*H*], 3.81 (3H, s, O*Me*), 4.92 [1H, q, *J* 7.2, C(α)*H*], 5.14–5.24 [2H, m, C(2′)H_2], 5.82 [1H, m, C(1′)*H*], 6.86–6.90 [2H, m, Ph(3)*H*, Ph(5)*H* C_6H_4OMe], 7.21–7.25 [2H, m, Ph(2)*H*, Ph(6)*H* C_6H_4OMe]; δ_C (100 MHz, $CDCl_3$) 19.3, 42.9, 51.2, 53.1, 55.2, 113.8, 118.3, 128.4, 132.3, 138.4, 158.9, 166.2; *m/z* APCI$^+$ 232.2 (MH$^+$, 100%), 135.1 ($C_9H_{11}O^+$, 60%); HRMS (ESI) $C_{14}H_{18}NO_2$ requires 231.1338; found 231.1332.

Preparation of (*R*)-4-vinylazetidin-2-one[25] 28

Following representative procedure 2, CAN (1.06 g, 1.95 mmol) and **27** (150 mg, 0.65 mmol) in MeCN–H_2O (5 : 1) (12 ml) gave, after work-up and purification by column chromatography on silica gel (hexane–Et_2O 1 : 1), **28** (44 mg, 69%) as a colourless oil; $[a]_D^{24}$ +47.0 (*c* 0.6, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.62 [1H, dd, $J_{3A,3B}$ 14.6, $J_{3A,4}$ 1.7, C(3)H_A], 3.03 [1H, dd, $J_{3B,3A}$ 14.6, $J_{3B,4}$ 5.1, C(3)H_B], 3.79–3.83 [1H, m, C(4)*H*], 5.14–5.24 [2H, m, C(2′)H_2], 5.82 [1H, m, C(1′)*H*], 6.00 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 19.3, 42.9, 51.2, 53.1, 55.2, 113.8, 118.3, 128.4, 132.3, 138.4, 158.9, 166.2; *m/z* (CI$^+$) 98.1 (MH$^+$, 100%).

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