ARTICLE

OBC
www.rsc.org/obc

Chiral oxime ethers in asymmetric synthesis.† *O*-(1-Phenylbutyl)-benzyloxyacetaldoxime, a versatile reagent for the asymmetric synthesis of protected 1,2-aminoalcohols, α-amino acid derivatives, and 2-hydroxymethyl nitrogen heterocycles including iminosugars

Tracey S. Cooper,[a] Alexander S. Larigo,‡[a] Pierre Laurent,[a] Christopher J. Moody*[a] and Andrew K. Takle[b]

[a] *Department of Chemistry, University of Exeter, Stocker Road, Exeter, UK EX4 4QD*
[b] *GlaxoSmithKline, New Frontiers Science Park North, Third Avenue, Harlow, UK CM19 5AW*

Received 11th January 2005, Accepted 4th February 2005
First published as an Advance Article on the web 28th February 2005

Addition of a range of organolithium and Grignard reagents to (*E*)-*O*-(1-phenylbutyl)benzyloxyacetaldoxime **1** in the presence of boron trifluoride diethyl etherate is highly diastereoselective. The resulting hydroxylamines **2** undergo N–O bond cleavage upon treatment with zinc–acetic acid or molybdenum hexacarbonyl to give, after *N*-protection, protected 1,2-aminoalcohols **3** in high enantiomeric purity. Debenzylation of **3a** and **3d** gave *N*-Boc (*R*)-alaninol and (*S*)-phenylalaninol respectively. The hydroxylamines **2** also serve as α-amino acid precursors, **2i** being converted into *N*-formyl-(*R*)-alaninyl-(*S*)-(4-bromo)phenylalanine ester **7**, the *N*-terminal dipeptide of a natural depsipeptide. The versatility of the 1,2-aminoalcohol derivatives was further illustrated by their conversion into 5-, 6- and 7-membered 2-hydroxymethyl nitrogen heterocycles **15**–**19** in high enantiomeric excess by a ring-closing metathesis reaction. Further reaction of the dihydropyrrole **15** gave the iminosugar 1,4-dideoxy-1,4-imino-D-ribitol.

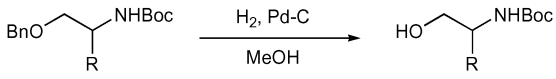
Introduction

Compounds with a chiral centre adjacent to nitrogen occur commonly in Nature and are also widely used as synthetic intermediates, ligands and chiral auxiliaries. Although many routes to this structural unit already exist, new stereoselective methods remain of interest. One powerful method for the construction of such asymmetric centres is the stereoselective addition to C=N bonds of imines, hydrazones, oximes, nitrones and sulfinimines,[2–7] and, in this area, we have described the addition reactions of *O*-(1-phenylbutyl) oxime ethers in the asymmetric synthesis of amines, α-amino acids and their β-homologues and a range of nitrogen heterocycles.[8] We now report that one oxime ether, *O*-(1-phenylbutyl)benzyloxyacetaldoxime **1**, is a particularly versatile intermediate for the asymmetric synthesis of a wide range of nitrogen-containing compounds.[9]

The (*E*)-oxime ether **1** was prepared in either enantiomeric form by reaction of the commercially available benzyloxyacetaldehyde with either (*R*)- or (*S*)-*O*-(1-phenylbutyl)hydroxylamine.[10] The (*E*) : (*Z*) ratio in the oxime ether formation was 49 : 22 (isolated yields), and chromatographic separation is unfortunately necessary since it is essential to use a single isomer in the subsequent reactions. Addition of a range of organolithium or Grignard reagents in the presence of boron trifluoride diethyl etherate in toluene at low temperature proceeded smoothly and gave the corresponding hydroxylamines **2** in reasonable yield and in good diastereomeric excess (Table 1). The only exception to this was the reaction involving the addition of allylmagnesium bromide that showed poor diastereoselectivity (42% de), although the major diastereomer was readily isolated in pure form. The stereochemistry at the new asymmetric centre was assigned on the basis of previous work, and on the subsequent transformations of the hydroxylamines **2**. The precise origin of the stereocontrol remains unclear, although we have proposed predictive models in earlier publications.[8]

The N–O bond in the hydroxylamines **2** was readily cleaved using either zinc in acetic acid with sonication,[11] as described in our previous publications,[1,12,13] or using molybdenum hexacarbonyl.[14,15] The resulting amines were not usually isolated but immediately protected as their *t*-butyl or benzyl carbamates. The protected 1,2-aminoalcohols **3** were formed in good yield and high enantiomeric excess as evidenced by HPLC on a chiral stationary phase (Table 2).[16] In most cases, the ee of the carbamate **3** mirrors the de of the hydroxylamine **2** although in case of **2a**/**3a** there is a significant difference, possibly as a result of using a different batch of starting hydroxylamine.

The benzyl protecting group can be readily removed to give *N*-Boc-protected 1,2-aminoalcohols. For example, the *O*-benzyl 1,2-aminoalcohols **3a** and **3e** were deprotected by hydrogenolysis to give the known compounds, *N*-Boc-(*R*)-alaninol **4a**[17] and *N*-Boc-(*S*)-phenylalaninol **4b**[18] (Scheme 1), thereby confirming the stereochemistry of the original addition to the chiral oxime ether **1**.



3a R = Me
3e R = Bn

4a R = Me (70%)
4b R = Bn (83%)

Scheme 1

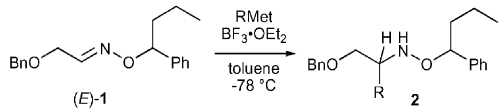
N-Boc-protected 1,2-aminoalcohols such as **4** are readily oxidized to the corresponding α-amino acid derivatives using reagents such as PDC in DMF,[19] $RuCl_3$–$NaIO_4$,[20] trichloroisocyanuric acid–TEMPO,[21] or the Dess–Martin periodinane followed by sodium chlorite.[22] However, we only investigated this in one case, namely the conversion of the hydroxylamine **2i** into the *N*-terminal dipeptide **7** of the depsipeptide polydiscamide A.[23] Thus cleavage of the N–O bond in hydroxylamine **2i** was followed by coupling to *N*-formyl-(*R*)-alanine[24] using DCC to give *N*-formyl-(*R*)-alaninyl-(*S*)-(4-bromo)phenylalaninol benzyl ether **5** in modest yield. Subsequent cleavage of the benzyl ether using boron trichloride gave the alcohol **6** that was oxidized with PDC in DMF to give the dipeptide **7** after esterification (Scheme 2).

The versatility of the 1,2-aminoalcohol derivatives obtained by stereoselective addition to *O*-(1-phenylbutyl)benzyloxyacetaldoxime **1** was further illustrated by the synthesis of a range

† Part 7. For part 6 see ref. 1.
‡ Deceased 30 August 2002.

DOI: 10.1039/b500390c

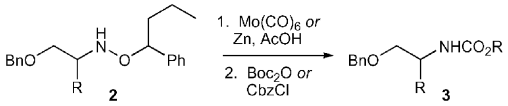
Table 1 Addition of organometallic reagents to *O*-(1-phenylbutyl)benzyloxyacetaldoxime **1**



Oxime configuration	Organometallic reagent	Hydroxylamine (configuration at new centre)	Yield (%)	De[a] (%)
R	MeLi	**2a** (*R*)	75	75
S	H_2C=CHLi	**2b** (*S*)	61	87
R	H_2C=CHLi	**2b** (*R*)	69	89
R	*n*-PrMgCl	**2c** (*R*)	82	90
R	*i*-PrMgCl	**2d** (*R*)	79	90
S	H_2C=$CHCH_2MgBr$	**2e** (*S*)	44[b]	42
R	*n*-BuLi	**2f** (*R*)	72	90
R	PhLi	**2g** (*R*)	56	>95
S	$PhCH_2MgBr$	**2h** (*S*)	83	90
S	4-$BrC_6H_4CH_2MgBr$	**2i** (*S*)	45	90
R	2-Lithiothiophene	**2j** (*S*)	81	80
R	2-Lithiothiazole	**2k** (*S*)	84	>95

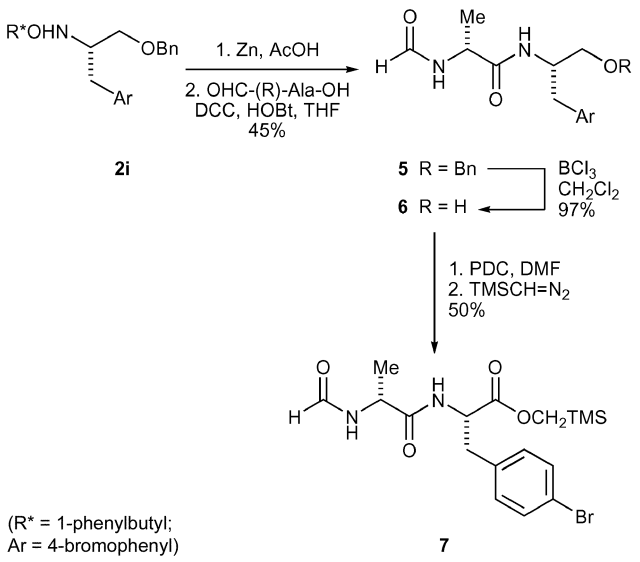
[a] Determined from the ^{1}H-NMR spectrum of crude hydroxylamine **2** (before chromatography) by integration of the C*H*NH signals. [b] Yield of the major diastereomer after separation.

Table 2 N–O bond cleavage in hydroxylamines **2** and protection of resulting amines as carbamates **3**

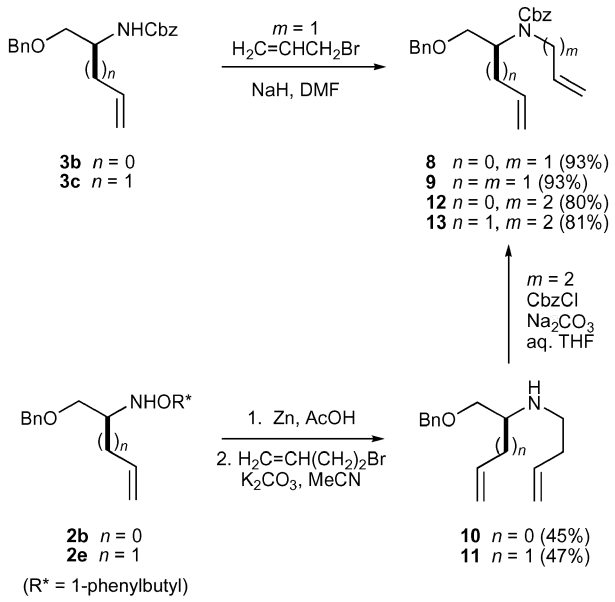


Hydroxylamine	Method[a]	R	R′	Protected 1,2-aminoalcohol **3** configuration		Yield (%)	Ee[b] (%)
2a	A	Me	*t*-Bu	**3a**	*R*	67	97
2b	B	H_2C=CH	Bn	**3b**	*S*	76	Nd[c]
2e[d]	B	H_2C=$CHCH_2$	Bn	**3c**	*S*	70	91
2f	A	*n*-Bu	*t*-Bu	**3d**	*R*	67	93
2h	A	Bn	*t*-Bu	**3e**	*S*	84	83
2i	B	4-$BrC_6H_4CH_2$	*t*-Bu	**3f**	*S*	53	97
2k	A	2-Thiazolyl	*t*-Bu	**3g**	*S*	77	98

[a] Method A: $Mo(CO)_6$, MeCN; Method B: Zn, AcOH, ultrasound. [b] Determined by HPLC on ChiralCel OD using hexane–isopropanol (85 : 15 to 95 : 5) as eluant. [c] Nd = not determined [d] The pure major diastereomer was used in this reaction.



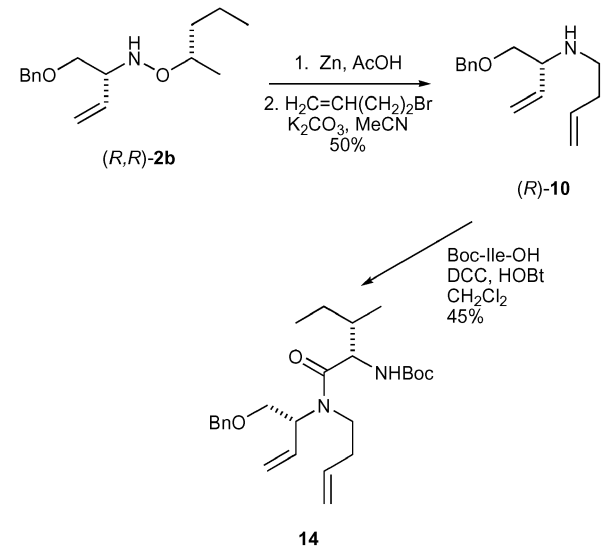
Scheme 2



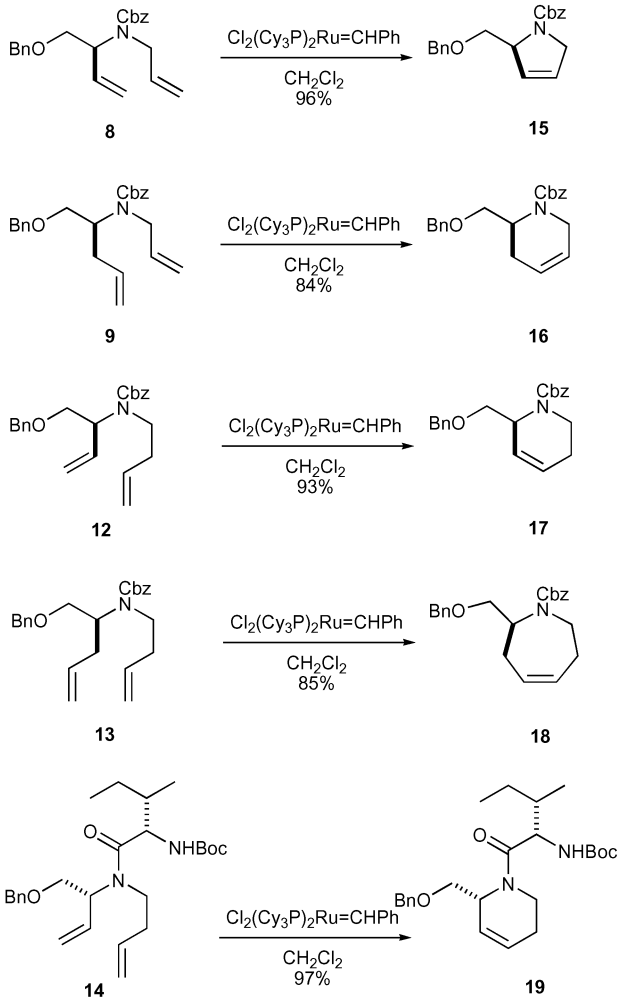
Scheme 3

of nitrogen heterocycles (Schemes 3–6). This was conveniently achieved by the incorporation of a second unsaturated sidechain (allyl or butenyl) into the derivatives obtained by addition of vinyl and allyl nucleophiles, thereby setting up dienyl systems for ring-closure by a ring-closing metathesis (RCM) reaction.[25]

Thus *N*-allylation of the benzyl carbamates **3b** and **3c** gave the corresponding (*S*)-*N*-allyl derivatives **8** and **9** in good yield. Attempted reaction of carbamates **3b** and **3c** with 4-bromobutene under similar conditions was unsatisfactory, and therefore the



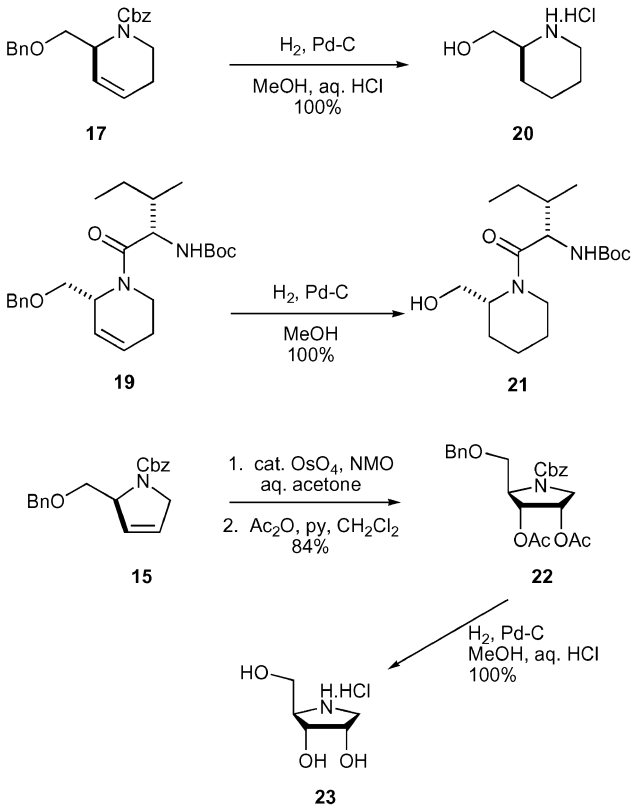
Scheme 4



Scheme 5

RCM precursors **12** and **13** were prepared differently. The N–O bond in hydroxylamines **2b** and **2e** was cleaved as before, and the resulting amines were alkylated with 4-bromobutene to give the (*S*)-secondary amines **10** and **11**, protection of which with benzyl chloroformate gave the (*S*)-dienes **12** and **13** (Scheme 3). In a related sequence, hydroxylamine (*R*,*R*)-**2b** was converted into (*R*)-**10**, DCC-coupling of which with *N*-Boc isoleucine gave the RCM precursor **14** (Scheme 4).

The RCM reactions of the five dienes were carried out by stirring a dichloromethane solution of the diene with benzylidene-



Scheme 6

bis-(tricyclohexylphosphine)dichlororuthenium (10 mol%) (Grubbs' catalyst) at room temperature until complete consumption of starting material was observed by TLC. The 2-benzyloxymethyl-5-, -6-, and -7-membered heterocycles **15**–**19** were formed in excellent yield as shown in Scheme 5. Thus the dihydropyrrole **15**, the isomeric tetrahydropyridines **16** and **17**, the tetrahydroazepine **18** and the tetrahydropyridine **19** were all prepared by this method.

Some of the 2-benzyloxymethyl heterocycles formed in the RCM reaction were elaborated further as shown in Scheme 6. Catalytic hydrogenation of tetrahydropyridine **17** over palladium-on-carbon resulted in concomitant reduction of the double bond and hydrogenolysis of the benzyl ether protecting group to give (*S*)-piperidine-2-methanol **20**. Similarly, the tetrahydropyridine **19** gave the isoleucinyl piperidine **21**, a potential precursor (by oxidation of the hydroxymethyl group) of the isoleucinyl pipecolic acid dipeptide of the apicidins, naturally occurring cyclic peptides.[26] Finally, the dihydropyrrole **15** was used in a synthesis of 1,4-dideoxy-1,4-imino-D-ribitol **23**, a naturally occurring glycosidase inhibitor isolated from the mulberry tree *Morus alba*.[27–31] Thus reaction of the dihydropyrrole **15** with a catalytic amount of osmium tetroxide in the presence of *N*-methylmorpholine-*N*-oxide (NMO) resulted in dihydroxylation from the least hindered face to give, after acetylation, the protected iminosugar **22** (84% over two steps). Hydrogenolysis of **22** over palladium-on-carbon in methanolic hydrochloric acid gave 1,4-dideoxy-1,4-imino-D-ribitol **23** as its hydrochloride salt in quantitative yield (Scheme 6).

In summary, we have shown that the oxime ether **1** is a versatile reagent for the asymmetric synthesis of protected 1,2-aminoalcohols and nitrogen heterocycles.

Experimental

For general experimental details, see ref. 12. With the exception of compound **2e**, which was isolated as a single diastereomer, hydroxylamines **2** were characterized as diastereomeric mixtures; the NMR data refer to the major diastereomer.

(*E*)-(*S*)-(−)-*O*-(1-Phenylbutyl)benzyloxyacetaldoxime (*E*)-(*S*)-1

Obtained from the cleavage of (*S*)-(−)-*N*-(1-phenylbutoxy)-phthalimide[10] (10.17 mmol) and subsequent condensation of the hydroxylamine with benzyloxyacetaldehyde (10.17 mmol). The crude product was purified by column chromatography on silica gel, eluting with light petroleum–dichloromethane (1 : 2) to give the pure product as a colourless oil (49%); (Found: C, 77.0; H, 8.0; N, 4.7. $C_{19}H_{23}NO_2$ requires C, 76.7; H, 7.8; N, 4.7%); (Found: MH^+, 298.1806. $C_{19}H_{23}NO_2$ + H requires 298.1807); $[\alpha]_D^{24}$ −6.7 (*c* 0.90, $CHCl_3$); ν_{max} (film)/cm^{-1} 3063, 3032, 2960, 2935, 2868, 1496, 1450, 1363, 1091, 1020, 922, 738, 697; δ_H (300 MHz; $CDCl_3$) 7.54 (1 H, t, J = 6.8 Hz, N=CH), 7.31 (10 H, m, ArH), 5.09 (1 H, t, J 7.0, OCH), 4.44 (2 H, AB, J 12.5, CH_2Ph), 4.07 (2 H, m, CH_2CHN), 1.95 (1 H, m, CHH), 1.73 (1 H, m, CHH), 1.51–1.26 (2 H, m, CH_2Me), 0.95 (3 H, t, J 7.3, Me); δ_C (75 MHz; $CDCl_3$) 147.5 (CH), 142.8 (C), 137.9 (C), 128.8 (CH), 128.7 (CH), 128.4 (CH), 128.2 (CH), 127.8 (CH), 127.1 (CH), 85.6 (CH), 72.7 (CH_2), 67.1 (CH_2), 38.7 (CH_2), 19.3 (CH_2), 14.4 (Me); m/z (CI) 298 (MH^+, 4%), 174 (6), 133 (100), 117 (35), 107 (35), 105 (95), 92 (88), 77 (99), 51 (81).

Also formed was (*Z*)-(*S*)-*O*-(1-phenylbutyl)benzyloxyacetaldoxime (*Z*)-(*S*)-**1** as a colourless oil (22%); δ_H (300 MHz; $CDCl_3$) 7.30 (10 H, m, ArH), 6.89 (1 H, t, J = 3.6 Hz, N=CH), 5.07 (1 H, t, J 6.9, OCH), 4.57 (2 H, s, CH_2Ph), 4.43 (2 H, m, CH_2CHN), 1.92 (1 H, m, CHH), 1.71 (1 H, m, CHH), 1.49–1.24 (2 H, m, CH_2Me), 0.94 (3 H, t, J 7.4, Me); δ_C (75 MHz; $CDCl_3$) 150.7 (CH), 142.9 (C), 137.9 (C), 128.9 (CH), 128.7 (CH), 128.3 (CH), 128.2 (CH), 127.9 (CH), 126.8 (CH), 85.9 (CH), 73.6 (CH_2), 65.2 (CH_2), 38.7 (CH_2), 19.3 (CH_2), 14.4 (Me).

(*E*)-(*R*)-(+)-*O*-(1-Phenylbutyl)benzyloxyacetaldoxime (*E*)-(*R*)-1

Obtained from the cleavage of (*R*)-(+)-*N*-(1-phenylbutoxy)-phthalimide[10] (10.17 mmol) and subsequent condensation of the hydroxylamine with benzyloxyacetaldehyde (10.17 mmol). The crude product was purified by column chromatography on silica gel, eluting with light petroleum–dichloromethane (1 : 2) to give the pure product as a colourless oil (60%); $[\alpha]_D^{26}$ +11.2 (*c* 1.07, CH_2Cl_2); spectroscopic properties are identical to the (*S*)-enantiomer (*E*)-(*S*)-**1**.

General procedure for the addition of organometallics

The oxime ether **1** (3.9 mmol, 1 equiv.) was dissolved in toluene (10 mL) under nitrogen and cooled to −78 °C or −90 °C. Boron trifluoride etherate (11.8 mmol, 3 equiv.) was added and the mixture stirred for 15 min. The organometallic reagent (11.8 mmol, 3 equiv.) was added dropwise over 30 min at this temperature, and the mixture stirred until all starting material was consumed. The reaction mixture was quenched at this temperature with aqueous saturated ammonium chloride solution (10 mL), and allowed to warm to room temperature. The mixture was extracted with diethyl ether (3 × 15 mL), combined, dried (K_2CO_3), filtered and evaporated. The residue was purified by column chromatography on silica gel.

(2*R*,1′*R*)-1-Benzyloxymethyl-*N*-(1-phenylbutoxy)-2-propylamine 2a. Obtained from the addition of methyllithium to oxime (*E*)-(*R*)-**1** as a colourless oil (75%, 75% de); $[\alpha]_D^{18}$ +41.6 (*c* 1.4, $CHCl_3$); (Found: MH^+, 314.2131. $C_{20}H_{27}NO_2$ + H requires 314.2120); ν_{max} (film)/cm^{-1} 3238 (NH), 3011, 2965, 2873, 1449; δ_H (300 MHz; $CDCl_3$) 7.22 (10 H, m, ArH), 5.59 (1 H, br s, NH), 4.49 (1 H, t, J = 5.9 Hz, OCH), 4.38 (2 H, s, CH_2Ph), 3.35 (1 H, m, NCH), 3.23 (2 H, m, OCH_2), 1.46 (1 H, m, CHH), 1.34 (1 H, m, CHH), 1.23 (2 H, m, CH_2), 1.00 (3 H, t, J 6.2, Me), 0.86 (3 H, t, J 7.3, Me); δ_C (75 MHz; $CDCl_3$) 143.6 (C), 138.7 (C), 128.72 (CH), 128.69 (CH), 127.9 (2 × CH), 127.6 (CH), 126.9 (CH), 85.8 (CH), 73.4 (CH_2), 71.8 (CH_2), 56.1 (CH), 39.3 (CH_2), 19.6 (CH_2), 15.8 (Me), 14.5 (Me); m/z (CI) 314 (MH^+, 12%), 210 (4), 192 (3), 181 (69), 164 (7), 150 (37), 133 (100), 91 (65).

(2*S*,1′*S*)-(−)-1-Benzyloxy-*N*-(1-phenylbutoxy)-2-but-3-enylamine (*S*,*S*)-2b. Obtained from the addition of vinyllithium (6.05 mmol) (prepared from tetravinyltin and methyllithium[32]) to oxime (*E*)-(*S*)-**1** (1.85 mmol). The crude product was purified by column chromatography on silica gel, eluting with light petroleum–dichloromethane (1 : 2) to give the pure product as a colourless oil (61%, 87% de); (Found: C, 77.9; H, 9.0; N, 4.3. $C_{21}H_{27}NO_2$ requires C, 77.5; H, 8.4; N, 4.3%); (Found: MH^+, 326.2123. $C_{21}H_{27}NO_2$ + H requires 326.2120); $[\alpha]_D^{22}$ −42.5 (*c* 1.20, $CHCl_3$); ν_{max} (film)/cm^{-1} 3263 (NH), 3083, 3068, 3032, 2950, 2930, 2863, 1501, 1455, 1363, 1096, 1030, 994, 917, 738, 692; δ_H (300 MHz; $CDCl_3$) 7.31 (10 H, m, ArH), 5.78 (2 H, m, =CH, NH), 5.24 (2 H, m, $=CH_2$), 4.57 (1 H, dd, J = 7.6, 5.8 Hz, OCH), 4.46 (2 H, AB, J 12.3, CH_2Ph), 3.75 (1 H, m, NCH), 3.48 (1 H, dd, J 9.6, 4.3, OCHH), 3.39 (1 H, dd, J 9.6, 8.1, OCHH), 1.79 (1 H, m, CHH), 1.59–1.16 (3 H, m, CHH, CH_2), 0.89 (3 H, t, J 7.2, Me); δ_C (75 MHz; $CDCl_3$) 143.7 (C), 138.5 (C), 136.6 (CH), 128.8 (CH), 128.7 (CH), 128.06 (CH), 128.03 (CH), 127.7 (CH), 127.0 (CH), 118.3 (CH_2), 85.8 (CH), 73.5 (CH_2), 70.5 (CH_2), 63.9 (CH), 39.3 (CH_2), 19.6 (CH_2), 14.5 (Me); m/z (CI) 326 (MH^+, 10%), 194 (59), 193 (15), 162 (31), 133 (100), 119 (9), 107 (11), 91 (99).

(2*R*,1′*R*)-(+)-1-Benzyloxy-*N*-(1-phenylbutoxy)-2-but-3-enylamine (*R*,*R*)-2b. Obtained from the addition of vinyllithium (20.20 mmol) to oxime (*E*)-(*R*)-**1** (6.73 mmol). The crude product was purified by column chromatography on silica gel, eluting with light petroleum–dichloromethane (1 : 2) to give the pure product as a colourless oil (69%, 89% de); $[\alpha]_D^{23}$ +45.7 (*c* 1.05, $CHCl_3$); spectroscopic properties are identical to the enantiomer (*S*,*S*)-**2b**.

(2*R*,1′*R*)-1-Benzyloxy-*N*-(1-phenylbutoxy)-2-pentylamine 2c. Obtained from the addition of *n*-propylmagnesium chloride to oxime (*E*)-(*R*)-**1** as a colourless oil (82%, 90% de); $[\alpha]_D^{17}$ +57.4 (*c* 0.6, $CHCl_3$); (Found: MH^+, 342.2441. $C_{22}H_{31}NO_2$ + H requires 342.2433); ν_{max} (film)/cm^{-1} 3262 (NH), 3032, 2863, 1454; δ_H (300 MHz; $CDCl_3$) 7.45–7.08 (10 H, m, ArH), 5.56 (1 H, br s, NH), 4.45 (1 H, t, J = 5.9 Hz, OCH), 4.39 (2 H, AB, J 14.0, CH_2Ph), 3.45 (1 H, dd, J 9.5, 3.9, OCHH), 3.28 (1 H, dd, J 9.5, 6.5, OCHH), 2.99 (1 H, m, NCH), 1.74 (1 H, m, CHH), 1.26 (7 H, m, CHH, 3 × CH_2), 0.83 (6 H, m, 2 × Me); δ_C (75 MHz; $CDCl_3$) 143.9 (C), 139.1 (C), 129.7 (CH), 129.0 (2 × CH), 128.2 (CH), 127.9 (CH), 127.3 (CH), 85.8 (CH), 73.7 (CH_2), 70.4 (CH_2), 60.8 (NCH), 39.4 (CH_2), 32.3 (CH_2), 19.9 (CH_2), 19.8 (CH_2), 14.9 (Me), 14.7 (Me); m/z (CI) 342 (MH^+, 100%), 286 (22), 210 (89), 133 (9).

(2*R*,1′*R*)-1-Benzyloxy-3-methyl-*N*-(1-phenylbutoxy)-2-butylamine 2d. Obtained from the addition of isopropylmagnesium chloride to oxime (*E*)-(*R*)-**1** as a colourless oil (79%, 90% de); $[\alpha]_D^{19}$ +38.8 (*c* 1.6, $CHCl_3$); (Found: M^+, 341.2373. $C_{22}H_{31}NO_2$ requires 341.2355); ν_{max} (film)/cm^{-1} 3252 (NH), 3032, 2955, 2868, 1490, 1454; δ_H (300 MHz; $CDCl_3$) 7.23 (10 H, m, ArH), 6.15 (1 H, br s, NH), 4.47 (1 H, t, J = 5.9 Hz, OCH), 4.37 (2 H, AB, J 12.0, CH_2Ph), 3.47 (1 H, dd, J 9.7, 6.3, OCHH), 3.26 (1 H, dd, J 9.7, 7.3, OCHH), 2.83 (1 H, m, NCH), 1.84 (1 H, m, CHMe$_2$), 1.64 (1 H, m, CHH), 1.46 (1 H, m, CHH), 1.32 (2 H, m, CH_2), 0.86 (6 H, d, J 6.8, 2 × Me), 0.79 (3 H, t, J 7.2, Me); δ_C (75 MHz; $CDCl_3$) 143.8 (C), 138.8 (C), 128.7 (CH), 128.6 (CH), 127.9 (2 × CH), 127.6 (CH), 127.0 (CH), 85.3 (CH), 73.4 (CH_2), 67.8 (CH_2), 65.9 (CH), 39.1 (CH_2), 27.7 (CH), 20.1 (Me), 19.6 (CH_2), 18.8 (Me), 14.5 (Me); m/z (EI) 341 (M^+, 6%), 298 (10), 278 (8), 209 (22), 178 (87), 133 (100), 107 (29), 91 (83), 77 (26).

(2*S*,1′*S*)-(−)-1-Benzyloxy-*N*-(1-phenylbutoxy)-2-pent-4-enylamine 2e. Obtained from the addition of allylmagnesium bromide (3.03 mmol) to oxime (*E*)-(*S*)-**1** (1.01 mmol). The crude product was purified by column chromatography on silica gel, eluting with light petroleum–dichloromethane (1 : 2) to give the pure product as a colourless oil (44% of major

diastereoisomer, 42% de); (Found: C, 78.0; H, 8.8; N, 3.9. $C_{22}H_{29}NO_2$ requires C, 77.8; H, 8.6; N, 4.1%); (Found: M^+, 339.2209. $C_{22}H_{29}NO_2$ requires 339.2198); $[\alpha]_D^{24}$ −44.7 (*c* 0.76, $CHCl_3$); ν_{max} (film)/cm^{-1} 3478 (NH), 3063, 3027, 2960, 2925, 2863, 1496, 1450, 1358, 1102, 1025, 917, 733, 692; δ_H (300 MHz; $CDCl_3$) 7.30 (10 H, m, ArH), 5.79 (1 H, m, =CH), 5.67 (1 H, br s, NH), 5.05 (2 H, m, $=CH_2$), 4.55 (1 H, t, J = 6.8 Hz, OCH), 4.46 (2 H, AB, J 12.1, CH_2Ph), 3.50 (1 H, dd, J 9.6, 4.1, OC*H*H), 3.38 (1 H, dd, J 9.6, 7.0, OCH*H*), 3.17 (1 H, m, NCH), 2.34 (1 H, m, C*H*HCH=), 2.19 (1 H, m, CH*H*CH=), 1.80 (1 H, m, C*H*H), 1.55 (1 H, m, CH*H*), 1.48–1.20 (2 H, m, CH_2), 0.91 (3 H, t, J 7.4, Me); δ_C (75 MHz; $CDCl_3$) 143.5 (C), 138.7 (C), 135.6 (CH), 128.73 (CH), 128.69 (CH), 127.98 (CH), 127.96 (CH), 127.7 (CH), 127.0 (CH), 117.5 (CH_2), 85.7 (CH), 73.5 (CH_2), 69.8 (CH_2), 60.3 (CH), 39.1 (CH_2), 34.4 (CH_2), 19.6 (CH_2), 14.5 (Me); *m*/*z* (EI) 339 (M^+, 3%), 298 (3), 207 (24), 176 (23), 166 (96), 133 (88), 107 (48), 91 (100), 77 (39).

(2*R*,1′*R*)-1-Benzyloxy-*N*-(1-phenylbutoxy)-2-hexylamine 2f. Obtained from the addition of *n*-butyllithium to oxime (*E*)-(*R*)-**1** as a colourless oil (72%, 90% de); $[\alpha]_D^{24}$ +38.6 (*c* 1.1, $CHCl_3$); (Found: M^+, 355.2518. $C_{23}H_{33}NO_2$ requires 355.2511); ν_{max} (film)/cm^{-1} 3032, 2965, 2863, 1495, 1449; δ_H (300 MHz; $CDCl_3$) 7.21 (10 H, m, ArH), 5.22 (1 H, br s, NH), 4.67 (1 H, t, J = 5.7 Hz, OCH), 4.38 (2 H, AB, J 12.0, CH_2Ph), 3.42 (1 H, m, OC*H*H), 3.28 (1 H, m, OCH*H*), 2.98 (1 H, m, NCH), 1.70 (1 H, m, C*H*H), 1.47 (1 H, m, CH*H*), 1.26 (2 H, m, CH_2), 1.19 (6 H, m, 3 × CH_2), 0.84 (3 H, t, J 7.3, Me), 0.79 (3 H, t, J 4.0, Me); δ_C (75 MHz; $CDCl_3$) 143.6 (C), 138.8 (C), 128.7 (CH), 128.6 (CH), 127.94 (CH), 127.91 (CH), 127.6 (CH), 126.9 (CH), 85.5 (CH), 73.5 (CH_2), 70.1 (CH_2), 60.8 (CH), 39.2 (CH_2), 29.5 (CH_2), 28.7 (CH_2), 23.3 (CH_2), 19.6 (CH_2), 14.6 (Me), 14.4 (Me); *m*/*z* (EI) 355 (M^+, 4%), 223 (24), 192 (99), 174 (7), 150 (4), 133 (83), 107 (40), 91 (100), 77 (32).

(1*R*,1′*R*)-1-Benzyloxy-1-phenyl-*N*-(1-phenylbutoxy)ethylamine 2g. Obtained from the addition of phenyllithium to oxime (*E*)-(*R*)-**1** as a colourless oil (56%, >95%); $[\alpha]_D^{21}$ +45.8 (*c* 0.5, $CHCl_3$); (Found: MH^+, 376.2286. $C_{25}H_{29}NO_2$ + H requires 376.2277); ν_{max} (film)/cm^{-1} 3243 (NH), 3023, 2955, 2866, 1497, 1448; δ_H (300 MHz; $CDCl_3$) 7.21 (15 H, m, ArH), 5.89 (1 H, br s, NH), 4.37 (2 H, s, CH_2Ph), 4.30 (3 H, m, OCH, OCH_2), 3.39 (1 H, m, NCH), 1.47 (1 H, m, C*H*H), 1.24 (1 H, m, CH*H*), 0.85 (2 H, m, CH_2), 0.56 (3 H, t, J = 7.3 Hz, Me); δ_C (75 MHz; $CDCl_3$) 144.0 (C), 140.2 (C), 138.3 (C), 128.8–126.4 (9 × CH), 85.7 (CH), 73.5 (CH_2), 72.2 (CH_2), 65.5 (CH), 39.3 (CH_2), 19.4 (CH_2), 14.4 (Me); *m*/*z* (CI) 376 (MH^+, 14) 254 (19), 244 (41), 212 (57), 182 (7), 150 (8), 133 (100), 122 (23), 107 (68), 91 (99).

(2*S*,1′*S*)-1-Benzyloxy-3-phenyl-*N*-(1-phenylbutoxy)-2-propylamine 2h. Obtained from the addition of benzylmagnesium bromide to oxime (*E*)-(*S*)-**1** as a colourless oil (83%, 90% de); $[\alpha]_D^{21}$ −37.4 (*c* 0.8, $CHCl_3$); (Found: MH^+, 390.2454. $C_{26}H_{31}NO_2$ + H requires 390.2433); ν_{max} (film)/cm^{-1} 3233 (NH), 3032, 2954, 2868, 1496, 1448; δ_H (300 MHz; $CDCl_3$) 7.21 (15 H, m, ArH), 5.56 (1 H, br s, NH), 4.47 (1 H, t, J = 6.0 Hz, OCH), 4.35 (2 H, AB, J 11.9, OCH_2Ph), 3.40 (1 H, m, NCH), 3.31 (2 H, m, OCH_2), 2.86 (1 H, dd, J 11.9, 7.5, C*H*HPh), 2.59 (1 H, dd, J 11.9, 7.5, CH*H*Ph), 1.69 (1 H, m, C*H*H), 1.49 (1 H, m, CH*H*), 1.18 (2 H, m, CH_2), 0.82 (3 H, t, J 6.2, Me); δ_C (75 MHz; $CDCl_3$) 143.5 (C), 139.3 (C), 138.7 (C), 130.2–126.6 (9 × CH), 85.8 (CH), 73.6 (CH_2), 69.5 (CH_2), 62.4 (CH), 39.1 (CH_2), 36.1 (CH_2), 19.7 (CH_2), 14.5 (Me); *m*/*z* (CI) 390 (MH^+, 84%), 365 (3), 298 (37), 278 (33), 258 (100), 242 (42), 210 (32), 165 (31).

(2*S*,1′*S*)-1-Benzyloxy-3-(4-bromophenyl)-*N*-(1-phenylbutoxy)-2-propylamine 2i. Obtained from the addition of 4-bromobenzylmagnesium bromide to oxime (*E*)-(*S*)-**1** as a yellow oil (45%, 90% de); (Found: MH^+, 468.1534. $C_{26}H_{30}{}^{79}BrNO_2$ + H requires 468.1538); $[\alpha]_D^{26}$ −28.9 (*c* 1.38, $CHCl_3$); ν_{max} (film)/cm^{-1} 3062, 3021, 2934, 2868, 1490, 1449, 1357, 1203, 1014, 901, 691; δ_H (300 MHz; CDCl3) 7.40 (2 H, d, J = 8.2 Hz, ArH), 7.39 – 7.28 (10 H, m, ArH), 7.07 (2 H, d, J 8.2, ArH), 5.62 (1 H, br s, NH), 4.54 (1 H, dd, J 6.1, 7.7, OCH), 4.49 (2 H, dd, J 11.8, 22.5 CH_2Ar), 3.48 (1 H, dd, J 5.2, 9.4, C*H*HOCH$_2$Ph), 3.36 (1 H, dd, J 5.2, 9.4, CH*H*OCH$_2$Ph), 3.26 (1 H, m, *H*CNH), 2.87 (1 H, dd, J 7.0, 12.7, CH$_2$OC*H*HPh), 2.64 (1 H, dd, J 7.0, 12.7, CH$_2$OCH*H*Ph), 1.80 (1 H, m, C*H*H), 1.57 (1 H, m, CH*H*), 1.43 (1 H, m, C*H*H), 1.30 (1 H, m, CH*H*), 0.93 (3 H, t, J 7.3, Me); δ_C (75 MHz; $CDCl_3$) 142.9 (C), 138.1 (C), 137.9 (C), 131.4 (CH), 131.1 (CH), 130.9 (CH), 128.3 (CH), 127.8 (CH), 127.6 (CH), 127.4 (CH), 126.6 (CH), 120.0 (C), 85.3 (CH), 73.1 (CH_2), 68.9 (CH_2), 61.7 (CH), 38.6 (CH_2), 35.0 (CH_2), 19.2 (CH_2), 14.1 (Me); *m*/*z* (CI) 468/466 (MH^+, 46%), 320 (15), 166 (13), 150 (100), 133 (21), 108 (40), 91 (64), 78 (5).

(2*S*,1′*R*)-1-Benzyloxy-*N*-(1-phenylbutoxy)-1-(2-thienyl)ethylamine 2j. Obtained from the addition of 2-lithiothiophene to oxime (*E*)-(*R*)-**1** as a yellow oil (81%, 80% de); $[\alpha]_D^{24}$ +86.9 (*c* 1.0, $CHCl_3$); (Found: MH^+, 382.1835. $C_{23}H_{27}NO_2S$ + H requires 382.1841); ν_{max} (film)/cm^{-1} 3267 (NH), 3027, 2955, 2929, 1454, 1106; δ_H (300 MHz; $CDCl_3$) 7.31 (11 H, m, ArH), 7.01 (2 H, m, ArH), 5.98 (1 H, br, NH), 4.63 (1 H, m, OCH), 4.53 (1 H, m, NCH), 4.50 (2 H, s, CH_2Ph), 3.61 (2 H, m, OCH_2), 1.66 (1 H, m, C*H*H), 1.44 (1 H, m, CH*H*), 1.31 (2 H, m, CH_2), 0.78 (3 H, t, J = 7.3 Hz, Me); δ_C (75 MHz; $CDCl_3$) 143.7 (C), 143.5 (C), 138.2 (C), 128.8–124.9 (9 × CH), 85.9 (CH), 73.6 (CH_2), 72.0 (CH_2), 61.2 (CH), 39.1 (CH_2), 19.3 (CH_2), 14.3 (Me); *m*/*z* (CI) 382 (MH^+, 23%), 309 (4), 281 (10), 260 (17), 237 (36), 217 (58), 199 (7), 133 (32), 107 (13), 91 (100).

(1*S*,1′*R*)-1-Benzyloxy-*N*-(1-phenylbutoxy)-1-(2-thiazolyl)-ethylamine 2k. Obtained from the addition of 2-lithiothiazole to oxime (*E*)-(*R*)-**1** as a yellow oil (84%, >95% de); $[\alpha]_D^{18}$ +31.7 (*c* 2.3, $CHCl_3$); (Found: M^+, 382.1720. $C_{22}H_{26}N_2O_2S$ requires 382.1715); ν_{max} (film)/cm^{-1} 3262 (NH), 3037, 2960, 2960, 2868, 1501, 1460; δ_H (300 MHz; $CDCl_3$) 7.61 (1 H, d, J = 3.3 Hz, thiazole H-4), 7.16 (11 H, m, ArH, thiazole H-5), 5.96 (1 H, br s, NH), 4.60 (1 H, dd, J 8.9, 4.1, NCH), 4.51 (1 H, t, J 5.8, OCH), 4.35 (2 H, AB, J 12.0, CH_2Ph), 3.65 (1 H, dd, J 9.9, 4.1, OC*H*H), 3.46 (1 H, dd, J 9.9, 4.0, OCH*H*), 1.53 (1 H, m, C*H*H), 1.36 (1 H, m, CH*H*), 1.21 (2 H, m, CH_2), 0.65 (3 H, t, J 7.3, Me); δ_C (75 MHz; $CDCl_3$) 170.9 (C), 143.1 (C), 142.7 (CH), 137.9 (C), 128.8 (2 × CH), 128.2 (CH), 128.0 (CH), 127.8 (CH), 126.9 (CH), 119.5 (CH), 86.1 (CH), 73.6 (CH_2), 70.6 (CH_2), 63.5 (CH), 39.0 (CH_2), 19.3 (CH_2), 14.3 (Me); *m*/*z* (EI) 382 (M^+, 5%), 295 (3), 219 (15), 250 (25), 199 (11), 150 (7), 133 (38), 107 (58), 91 (100), 85 (25), 77 (32).

General procedure for the preparation of *N*-Boc-protected amines 3 (R = ^{t}Bu)

Hydroxylamine **2** (0.5 mmol) was dissolved in acetonitrile (8 mL) and water (2 mL). Molybdenum hexacarbonyl (0.5 mmol) was added and the mixture heated under reflux overnight. The reaction mixture was allowed to cool to room temperature, di-*tert*-butyl dicarbonate (2 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (catalyst) were added and the mixture was allowed to stir overnight. The solvent was removed *in vacuo* and the residue purified by column chromatography on silica gel eluting with ethyl acetate–light petroleum. The enantiomeric purity of the product was assessed by HPLC on a ChiralCel OD column using hexane–2-propanol (95 : 5) as eluant.

General procedure for the preparation of *N*-Cbz-protected amines 3 (R = Bn)

Zinc dust (15 mmol) was added to a solution of the hydroxylamine **2** (0.38 mmol) in acetic acid–water (1 : 1; 6 mL). The mixture was placed in a sonic bath at 40 °C until all the starting material was consumed (TLC, typically 1.5–4 h). The zinc was filtered off and rigorously washed with water and diethyl ether. The filtrate was extracted with diethyl ether (5×), the aqueous layer was basified to pH 12 with aqueous sodium

hydroxide solution (2 M) and a little saturated ammonium chloride solution was added to disperse the emulsion. The solution was further extracted with dichloromethane (3×). The dichoromethane organic layers were combined and evaporated. The residue was dissolved in THF–water (1 : 1; 20 mL) and sodium carbonate (1.52 mmol) was added. The solution was cooled to 0 °C and benzyl chloroformate (0.50 mmol) added dropwise. The mixture was allowed to warm to room temperature and was stirred overnight. The THF was evaporated under reduce pressure. Diethyl ether (10 mL) was added, the layers were separated, and the aqueous layer was extracted with further portions of diethyl ether (3×). The organic layers were combined, dried ($MgSO_4$), filtered and evaporated. The enantiomeric purity of the product was assessed by HPLC on a ChiralCel OD column using hexane–2-propanol (85 : 15 to 95 : 5) as eluant, flow rate 1 mL min^{-1}.

(*R*)-1-Benzyloxy-*N*-*tert*-butoxycarbonyl-2-propylamine 3a. Obtained as a colourless oil (67%, 97% ee) (lit.,[20] no data); $[\alpha]_D^{19}$ +24.5 (*c* 0.5, $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 7.24 (5 H, m, ArH), 4.65 (1 H, br s, NH), 4.46 (2 H, AB, *J* = 12.0 Hz, C*H*$_2$Ph), 3.81 (1 H, br, NCH), 3.38 (2 H, m, OCH_2), 1.36 (9 H, s, CMe_3), 1.11 (3 H, d, *J* 6.7, Me); HPLC: hexane–2-propanol (95 : 5), t_R = 8.8 (major) and 11.9 min.

(*S*)-(−)-1-Benzyloxy-*N*-benzyloxycarbonyl-2-but-3-enylamine 3b. Obtained as a colourless oil (76%) that slowly solidifies; mp 39–40 °C; (Found: MH^+, 312.1606. $C_{19}H_{21}NO_3$ + H requires 312.1600); $[\alpha]_D^{22}$ −27.2 (*c* 0.92, $CHCl_3$); ν_{max} (film)/cm^{-1} 3416 (NH), 3324, 3088, 3063, 3027, 2940, 2894, 2853, 1716 (C=O), 1496, 1450, 1404, 1342, 1219, 1096, 912, 733, 687; δ_H (300 MHz; $CDCl_3$) 7.34 (10 H, m, ArH), 5.89 (1 H, ddd, *J* = 17.2, 10.4, 5.5 Hz, =CH), 5.33–5.07 (5 H, m, C*H*$_2$Ph, =CH_2, NH), 4.54 (2 H, AB, *J* 12.2, C*H*$_2$Ph), 4.41 (1 H, br, NCH), 3.56 (2 H, m, NCHC*H*$_2$); δ_C (75 MHz; $CDCl_3$) 156.3 (C), 138.2 (C), 136.9 (C), 136.4 (CH), 128.94 (CH), 128.86 (CH), 128.5 (2 × CH), 128.2 (CH), 128.1 (CH), 116.5 (CH_2), 73.7 (CH_2), 72.3 (CH_2), 67.2 (CH_2), 53.5 (CH); *m*/*z* (CI) 312 (MH^+, 23%), 268 (92), 204 (29), 181 (32), 91 (100).

(*S*)-(−)-1-Benzyloxy-*N*-benzyloxycarbonyl-2-pent-4-enylamine 3c. Obtained as a colourless oil (70%, 91% ee); (Found: MH^+, 326.1758. $C_{20}H_{23}NO_3$ + H requires 326.1756); $[\alpha]_D^{26}$ −10.8 (*c* 0.83, $CHCl_3$); ν_{max} (film)/cm^{-1} 3416 (NH), 3329, 3068, 3027, 2940, 2863, 1716 (C=O), 1501, 1235, 1112, 1055, 912, 738, 697; δ_H (300 MHz; $CDCl_3$) 7.32 (10 H, m, ArH), 5.76 (1 H, m, =CH), 5.05 (5 H, m, C*H*$_2$Ph, =CH_2, NH), 4.51 (2 H, AB, *J* = 12.0 Hz, C*H*$_2$Ph), 3.89 (1 H, br, NCH), 3.50 (2 H, m, NCHC*H*$_2$), 2.37 (2 H, m, C*H*$_2$CH=); δ_C (75 MHz; $CDCl_3$) 156.3 (C), 138.4 (C), 137.0 (C), 134.7 (CH), 128.9 (CH), 128.8 (CH), 128.48 (CH), 128.46 (CH), 128.1 (CH), 128.0 (CH), 118.3 (CH_2), 73.6 (CH_2), 71.3 (CH_2), 67.0 (CH_2), 50.8 (CH), 36.8 (CH_2); *m*/*z* (CI) 326 (MH^+, 25%), 282 (100), 240 (25), 181 (39), 91 (75); HPLC: hexane–2-propanol (85 : 15), t_R = 8.1 and 10.4 (major) min.

(*R*)-1-Benzyloxy-*N*-*tert*-butoxycarbonyl-2-hexylamine 3d. Obtained as a colourless oil (63%, 93% ee); $[\alpha]_D^{23}$ +17.6 (*c* 0.9, $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 7.23 (5 H, m, ArH), 4.61 (1 H, br s, NH), 4.43 (2 H, AB, *J* = 12.1 Hz, C*H*$_2$Ph), 3.64 (1 H, br, NCH), 3.39 (2 H, m, OCH_2), 1.37 (9 H, s, 3 × Me), 1.22 (6 H, m, 3 × CH_2), 0.81 (3 H, t, *J* 6.7, Me); δ_C (75 MHz; $CDCl_3$) 156.0 (C), 137.8 (C), 128.8 (CH), 128.0 (CH), 127.9 (CH), 79.4 (C), 73.4 (OCH_2), 72.4 (OCH_2), 50.8 (CH), 32.3 (CH_2), 28.8 (Me), 28.6 (CH_2), 23.0 (CH_2), 14.4 (Me).

(*S*)-1-Benzyloxy-*N*-*tert*-butoxycarbonyl-3-phenyl-2-propylamine 3e. Obtained as a colourless oil (84%, 88% ee); $[\alpha]_D^{19}$ −22.0 (*c* 0.5, $CHCl_3$) {lit.,[33] $[\alpha]_D^{28}$ −4.9 (*c* 0.45, $CHCl_3$)}; ν_{max} (film)/cm^{-1} 3375 (NH), 2929, 2852, 1685 (C=O), 1527; δ_H (300 MHz; $CDCl_3$) 7.28 (10 H, m, ArH), 4.90 (1 H, br d, *J* = 8.3 Hz, NH), 4.50 (2 H, AB, *J* 12.0, OC*H*$_2$Ph), 3.96 (1 H, br, NCH), 3.39 (2 H, m, OCH_2), 2.88 (2 H, m, C*H*$_2$Ph), 1.43 (9 H, s, CMe_3); δ_C (75 MHz; $CDCl_3$) 155.8 (C), 138.6 (C), 138.5 (C), 129.9 (CH), 128.8 (CH), 128.7 (CH), 128.2 (2 × CH), 127.6 (CH), 79.7 (C), 73.6 (CH_2), 70.5 (CH_2), 52.1 (CH), 38.3 (CH_2), 28.8 (Me); HPLC: hexane–2-propanol (90 : 10), t_R = 8.1 and 8.7 (major) min.

(*S*)-1-Benzyloxy-3-(4-bromophenyl)-*N*-*tert*-butoxycarbonyl-2-propylamine 3f. Obtained as a colourless solid (53%, 97% ee), mp 72–73 °C; Found: MH^+, 420.1171. $C_{21}H_{26}{}^{79}BrNO_3$ + H requires 420.1174); $[\alpha]_D^{26}$ −4.0 (*c* 1.04, CH_3Cl); ν_{max} (KBr)/cm^{-1} 3359, 2919, 2847, 1685, 1526, 1490, 1362, 1168; δ_H (300 MHz; $CDCl_3$) 7.40–7.30 (5 H, m, ArH), 7.35 (2 H, d, *J* = 8.2 Hz, ArH), 7.03 (2 H, d, *J* 8.2, ArH), 4.93 (1 H, d, *J* 8.2, NH), 4.48 (2 H, dd, *J* 11.8, 24.4, C*H*$_2$OCH_2Ph), 3.90 (1 H, m, *H*CNH), 3.39 (1 H, dd, *J* 3.9, 9.3, CH_2OC*H*HPh), 3.35 (1 H, dd, *J* 3.9, 9.3, CH_2OCH*H*Ph), 2.83 (2 H, m, C*H*$_2$Ar), 1.45 (9 H, s, 3 × Me); δ_C (75 MHz; $CDCl_3$) 155.3 (C), 137.9 (C), 137.2 (C), 131.4 (CH), 131.2 (CH), 127.86 (CH), 127.83 (CH), 126.4 (CH), 120.2 (C), 73.3 (CH_2), 69.9 (CH_2), 51.5 (CH), 37.3 (C), 27.9 (Me), 27.8 (CH_2); *m*/*z* (CI), 420/418 (MH^+, 3%), 386 (10), 339 (8), 322 (19), 193 (13), 161 (25), 129 (100), 97 (64), 90 (33).

(*S*)-2-Benzyloxy-*N*-*tert*-butoxycarbonyl-1-(2-thiazolyl)ethylamine 3g. Obtained as a yellow oil (0.129 g, 77%, 98% ee); $[\alpha]_D^{23}$ −41.7 (*c* 1.2, $CHCl_3$); (Found: C, 69.6; H, 7.3; N, 7.3. $C_{17}H_{22}N_2O_3S$ requires C, 69.1, H, 7.0; N, 7.3%); (Found: M^+, 334.1354. $C_{17}H_{22}N_2O_3S$ requires 334.1351); ν_{max} (film)/cm^{-1} 3324 (NH), 2975, 2919, 2863, 1936, 1716 (C=O); δ_H (300 MHz; $CDCl_3$) 7.65 (1 H, d, *J* = 3.4 Hz, thiazole H-4), 7.19 (6 H, m, ArH, thiazole H-5), 5.61 (1 H, br, NH), 5.15 (1 H, br t, *J* 3.4, NCH), 4.39 (2 H, AB, *J* 12.0, C*H*$_2$Ph), 3.88 (1 H, br, OC*H*H), 3.75 (1 H, dd, 9.5, 4.6, OCH*H*), 1.38 (9 H, s, CMe_3); δ_C (75 MHz; $CDCl_3$) 171.5 (C), 155.5 (C), 143.0 (CH), 138.0 (C), 128.9 (CH), 128.2 (CH), 128.0 (CH), 119.5 (CH), 80.6 (C), 73.7 (CH_2), 72.2 (CH_2), 53.2 (CH), 28.7 (Me); *m*/*z* (EI) 334 (M^+, 4%), 278 (86), 230 (43), 157 (87), 139 (77), 108 (14), 91 (98), 85 (21); HPLC: hexane–2-propanol (90 : 10), t_R = 3.8 and 8.7 (major) min.

General procedure for the preparation of *N*-Boc-protected aminoalcohols 4

The *O*-benzyl *N*-Boc-amine **3** (0.2 mmol) and 10% Pd/C (cat.) were stirred vigorously in methanol (2 mL) under an atmosphere of hydrogen until all starting material had been consumed (as evidenced by TLC analysis). The solvent was removed *in vacuo* and the residue purified by column chromatography on silica gel eluting with dichloromethane–methanol.

(*R*)-*N*-*tert*-Butoxycarbonyl-1-hydroxy-2-propylamine (*N*-Boc-alaninol) 4a. Obtained by hydrogenolysis of **3a** as a colourless solid (0.0265 g, 70%, 96% ee), mp 49–50 °C (lit.,[17] mp 52–53 C); $[\alpha]_D^{19}$ +8.6 (*c* 0.8, $CHCl_3$) {lit.,[17] $[\alpha]_D^{26}$ +10.0 (*c* 1.0, MeOH)}; δ_H (300 MHz; MeOD) 4.65 (1 H, br s, NH), 3.76 (1 H, br, CH), 3.55 (1 H, A′AB, *J* = 10.8, 3.7 Hz, OC*H*H), 3.44 (1 H, AA′B, *J* 10.8, 4.6, OCH*H*), 2.68 (1 H, br s, OH), 1.44 (9 H, s, 3 × Me), 1.13 (3 H, d, *J* 6.8, Me).

(*S*)-*N*-*tert*-Butoxycarbonyl-1-hydroxy-3-phenyl-2-propylamine (*N*-Boc-phenylalaninol) 4b. Obtained by hydrogenolysis of **3e** as a colourless solid (0.0427 g, 83%, 88% ee), mp 89–91 °C (lit.,[18] mp 91–92 °C); $[\alpha]_D^{17}$ −32.4 (*c* 1.0, $CHCl_3$) {lit.,[18] $[\alpha]_D^{25}$ −25.0 (*c* 1.0, MeOH)}; δ_H (300 MHz; $CDCl_3$) 7.26–7.13 (5 H, m, ArH), 4.74 (1 H, d, *J* = 6.9 Hz, NH), 3.81 (1 H, br, CH), 3.60 (1 H, A′AB, *J* 10.1, 3.7, OCH*H*), 3.50 (1 H, AA′B, *J* 10.1, 5.3, OC*H*H), 2.78 (2 H, d, *J* 7.2, $PhCH_2$), 2.23 (1 H, br s, OH), 1.34 (9 H, s, CMe_3).

(+)-*N*-Formyl-(*R*)-alaninyl-(*S*)-(4-bromo)phenylalaninol benzyl ether 5

N-Formyl-(*R*)-alanine[24] (0.20 g, 1.86 mmol) and (*S*)-1-benzyloxy-3-(4-bromophenyl)-2-propylamine (0.60 g, 1.86 mmol) [obtained from the Zn–acetic acid cleavage of (2*S*,1′*S*)-1-benzyloxy-3-(4-bromophenyl)-*N*-(1-phenylbutoxy)-2-propylamine **2i**] were dissolved in THF (10 mL) and stirred at 0 °C together with HOBT (*N*-hydroxybenzotriazole; 0.25 g, 1.86 mmol) and DCC (0.38 g, 1.86 mmol). The mixture was then allowed to warm to room temperature and was stirred for 20 h. The product was subjected to an acid–base extraction, dried, evaporated and recrystallized from acetone and hexane to give the *title compound* as a colourless solid (0.35 g, 45%); mp 150–151 °C; (Found: MH^+, 419.0967. $C_{20}H_{23}{}^{79}BrN_2O_3$ + H requires 419.0970); $[a]_D{}^{21}$ + 7.8 (*c* 0.65, MeOH); ν_{max} (KBr)/cm^{-1} 3279, 1694, 1564, 1528, 1451, 1385, 1215, 1125; δ_H (300 MHz; $CDCl_3$) 8.10 (1 H, s, HCO), 7.37 − 7.24 (5 H, m, ArH), 7.30 (2 H, d, *J* 8.3, ArH), 7.02 (2 H, d, *J* 8.3, ArH), 6.32 (1 H, m, NH), 6.25 (1 H, m, NH), 4.46 (2 H, m, CH_2Ph), 4.46 (1 H, m, C*H*Me), 4.24 (1 H, m, C*H*CH_2Ar), 3.40 (2 H, d, *J* 3.6, CH_2OCH_2Ph), 2.85 (1 H, dd, *J* 7.0, 13.0, C*H*HAr), 2.80 (1 H, dd, *J* 7.0, 13.0, CH*H*Ar), 1.26 (3 H, d, *J* 7.0, Me); δ_C (75 MHz; $CDCl_3$) 171.1 (C), 160.5 (C), 137.6 (C), 136.7 (C), 131.4 (CH), 131.0 (CH), 128.5 (CH), 127.9 (CH), 127.9 (CH), 120.4 (C), 73.3 (CH_2), 69.6 (CH_2), 50.2 (CH), 47.5 (CH), 36.9 (CH_2), 18.8 (Me); *m*/*z* (ES), 421/419 (MH^+, 14%), 337 (10), 325 (4), 271 (6), 259 (11), 221 (9), 130 (28), 100 (39), 98 (100), 84 (98), 68 (58), 66 (39), 52 (15), 35 (83).

(+)-*N*-Formyl-(*R*)-alaninyl-(*S*)-(4-bromo)phenylalaninol 6

(+)-*N*-Formyl-(*R*)-alaninyl-(*S*)-4-bromphenylalaninol benzyl ether **5** (12.5 mg, 0.03 mmol) in dry dichloromethane (3 mL) was treated with a solution of boron trichloride in dichloromethane (1 M; 0.6 mL, 0.6 mmol) at 0 °C. The mixture was then allowed to warm to room temperature and stirred for 2 h. The reaction was cautiously quenched with water (2 mL) and the product extracted with ethyl acetate (3 × 10 mL), dried ($MgSO_4$) and purified by trituration with ether to give the *title compound* as a colourless solid (9.5 mg, 97%); (Found: MH^+, 329.0501. $C_{13}H_{17}{}^{79}BrN_2O_3$ + H requires 329.5000); mp 210–211 °C; $[a]_D{}^{24}$ + 3.0 (*c* 0.5, MeOH); ν_{max} (KBr)/cm^{-1} 3412, 1632, 1398, 1112, 618; δ_H (300 MHz; CD_3OD) 8.08 (1 H, s, CHO), 7.41 (2 H, d, *J* 8.2, ArH), 7.09 (2 H, d, *J* 8.2, ArH), 4.37 (1 H, q, 6.8, C*H*Me), 4.07 (1 H, m, *H*CCH_2Ar), 3.67 (1 H, dd, *J* 4.1, 11.4, C*H*HOH), 3.65 (1 H, dd, *J* 4.1, 11.4, CH*H*OH), 2.85 (1 H, dd, *J* 7.5, 13.9, C*H*HAr), 2.77 (1 H, dd, *J* 7.5, 13.9, CH*H*Ar), 1.20 (3 H, d, *J* 7.1, Me); 2 × NH and OH not observed; δ_C (75 MHz; CD_3OD) 174.7 (C), 163.8 (C), 139.7 (C), 133.6 (CH), 132.9 (CH), 121.6 (C), 64.9 (CH_2), 54.5 (CH), 49.9 (CH), 37.9 (CH_2), 19.2 (Me); *m*/*z* (CI), 329/327 (MH^+, 7%), 313 (18), 311 (34), 299 (78), 297 (100), 295 (28), 260 (33), 258 (41), 219 (40), 197 (27), 168 (43), 139 (17), 116 (26), 115 (8).

(+)-*N*-Formyl-(*R*)-alaninyl-(*S*)-4-bromphenylalanine trimethylsilylmethyl ester 7

To a solution of (+)-*N*-formyl-(*R*)-alanine-(*S*)-4-bromphenylalaninol **6** (100 mg, 0.3 mmol) in anhydrous DMF (10 mL), pyridinium dichromate (323 mg, 1.5 mmol) was added and stirred at room temperature for 5 h. The mixture was diluted with water (10 mL), the aqueous layer acidified with citric acid and the product extracted with ethyl acetate, dried ($MgSO_4$) and concentrated. The residue was dissolved in anhydrous DMF and treated with excess TMS diazomethane and stirred overnight. The product was concentrated and purified by flash chromatography to give the *title compound* as a colourless oil (62 mg, 50%); (Found: MH^+, 429.0843. $C_{17}H_{25}{}^{79}BrN_2O_4Si$ + H requires 429.0845); $[a]_D{}^{24}$ +13.9 (*c* 1.15, MeOH); ν_{max} (film)/cm^{-1} 3405, 3298, 3052, 2955, 1731, 1654, 1521, 1383, 1250, 1203, 1009, 850; δ_H (300 MHz; $CDCl_3$) 8.05 (1 H, s, HCO), 7.37 (2 H, d, *J* = 8.3 Hz, ArH), 7.06 (1 H, d, *J* 7.9, NH), 6.98 (2 H, d, *J* 8.3, ArH), 6.80 (1 H, d, *J* 7.2, NH), 4.78 (1 H, m, CH), 4.53 (1 H, m, CH), 3.78 (1 H, d, *J* 14.0, C*H*HTMS), 3.76 (1 H, d, *J* 14.0, CH*H*TMS), 3.10 (1 H, dd, *J* 6.6, 14.0, C*H*HAr), 2.94 (1 H, dd, *J* 6.6, 14.0, CH*H*Ar), 1.24 (3 H, d, *J* 6.9, CH*Me*), 0.00 (9 H, s, 3 × Me); δ_C (75 MHz; $CDCl_3$) 172.2 (C), 171.7 (C), 161.4 (C), 134.9 (C), 131.6 (CH), 130.9 (CH), 121.1 (C), 59.2 (CH_2), 53.2 (CH), 47.6 (CH), 37.4 (CH_2), 18.6 (Me), 0.0 (TMS); *m*/*z* (ES) 431/429 (MH^+, 36%), 416 (13), 415 (60), 413 (72), 395 (25), 316 (40), 198 (4), 170 (5), 91 (7), 73 (100), 72 (38), 45 (23), 44 (73).

Preparation of ring-closing metathesis precursors

***N*-Allylation of Cbz-amines 3b and 3c.** Sodium hydride (0.42 mmol) was suspended in dry DMF (1 mL) and cooled to 0 °C under nitrogen. A solution of the Cbz-amine **3b/3c** (0.21 mmol) in dry DMF (1 mL) was added and the reaction mixture was allowed to warm to room temperature. After 30 min, the reaction mixture was re-cooled to 0 °C. Allyl bromide (0.04 mL, 0.42 mmol) was added and the reaction mixture was allowed to warm to room temperature. After TLC analysis showed that all starting material had been consumed, aqueous saturated ammonium chloride solution (0.5 mL) was added and the mixture was extracted with diethyl ether (3×), dried (Na_2SO_4), filtered and evaporated under reduced pressure.

(*S*)-(+)-*N*-Allyl-1-benzyloxy-*N*-benzyloxycarbonyl-2-but-3-enylamine 8. Obtained from the *N*-allylation of Cbz-amine **3b** (0.52 mmol) and purification by column chromatography on silica gel eluting with diethyl ether–light petroleum (5 : 9) as a colourless oil (93%); (Found: MH^+, 352.1908. $C_{22}H_{25}NO_3$ + H requires 352.1912); $[a]_D{}^{22}$ +8.9 (*c* 1.23, $CHCl_3$); ν_{max} (film)/cm^{-1} 3083, 3063, 3032, 2976, 2935, 2858, 1696 (C=O), 1496, 1455, 1409, 1352, 1322, 1245, 1204, 1107, 1030, 989, 917, 769, 737, 692; δ_H (400 MHz; C_6D_6, 80 °C) 7.31 (2 H, t, *J* 6.3, ArH), 7.19 (8 H, m, ArH), 5.93 (2 H, m, 2 × =CH), 5.21 (2 H, s, CH_2Ph), 5.20–4.99 (4 H, m, 2 × =CH_2), 4.83 (1 H, br q, *J* 6.0, NCH), 4.39 (2 H, AB, *J* 12.1, CH_2Ph), 4.01 (1 H, dd, *J* 16.0, 5.3, NC*H*H), 3.90 (1 H, dd, *J* 16.0, 5.8, NCH*H*), 3.75 (1 H, t, *J* 9.6, OC*H*H), 3.61 (1 H, dd, *J* 9.8, 5.8, OCH*H*); δ_C (100 MHz; C_6D_6, 80 °C) 155.8 (C), 138.7 (C), 137.4 (C), 135.9 (CH), 135.1 (CH), 128.2 (CH), 127.9 (CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 127.4 (CH), 116.7 (CH_2), 115.5 (CH_2), 72.9 (CH_2), 70.8 (CH_2), 66.9 (CH_2), 59.1 (CH), 48.1 (CH_2); *m*/*z* (ES) 720 (2 M + NH_4, 62%), 647 (12), 369 (M + NH_4, 95), 352 (MH^+, 100).

(*S*)-(+)-*N*-Allyl-1-benzyloxy-*N*-benzyloxycarbonyl-2-pent-4-enylamine 9. Obtained from the *N*-allylation of Cbz-amine **3c** (0.28 mmol) and purification by column chromatography on silica gel eluting with ether-light petroleum (1:2) as a colourless oil (93%); (Found: MH^+, 366.2061. $C_{23}H_{27}NO_3$ + H requires 366.2069); $[a]_D{}^{23}$ + 8.2 (*c* 0.97, $CHCl_3$); ν_{max} (film)/cm^{-1} 3068, 3032, 2976, 2935, 2858, 1696 (C=O), 1455, 1404, 1358, 1245; δ_H (300 MHz; $CDCl_3$) *two rotamers* 7.32 (10 H, m, ArH), 5.77 (2 H, m, 2 × =CH), 5.21–4.96 (6 H, m, 2 × =CH_2, CH_2Ph), 4.42 (2 H, m, CH_2), 4.22 (1 H, m, NCH), 3.89 (2 H, m, CH_2), 3.55 (2 H, m, CH_2), 2.35 (2 H, m, CH_2CH=); δ_C (75 MHz; $CDCl_3$) *two rotamers* 156.8 (C), 156.7 (C), 138.6 (C), 138.5 (C), 137.3 (C), 137.2 (C), 136.1 (CH), 135.8 (CH), 135.3 (CH), 135.1 (CH), 128.8–128.0 (several overlapping CH), 117.8 (CH_2), 117.7 (CH_2), 116.6 (CH_2), 116.3 (CH_2), 73.3 (CH_2), 71.4 (CH_2), 71.1 (CH_2), 67.5 (CH_2), 67.3 (CH_2), 56.7 (CH), 56.6 (CH), 48.1 (CH_2), 47.8 (CH_2), 35.1 (CH_2), 34.5 (CH_2); *m*/*z* (CI) 366 (MH^+, 35%), 322 (78), 280 (30), 258 (43), 200 (25), 181 (20), 168 (18), 119 (14), 91 (100).

General procedure for the *N*-alkylation of primary amines

Zinc dust (18.88 mmol) was added to a solution of the hydroxylamine **2** (0.47 mmol) in acetic acid-water (8 mL, 1:1). The mixture was placed in a sonic bath at 40 °C until all the

starting material was consumed (TLC; typically 1.5–4 h). The zinc was filtered and rigorously washed with water and ether. The filtrate was extracted with ether (5x), the aqueous layer was basified to pH 12 with aqueous sodium hydroxide solution (4 M) and a little saturated ammonium chloride solution was added to disperse the emulsion. The solution was further extracted with dichloromethane (3x). The dichloromethane organic layers were combined and evaporated. The crude amine (0.47 mmol) was dissolved in acetonitrile (5 mL) and potassium carbonate (0.50 mmol) and 4-bromobut-1-ene (0.80 mmol) were added to the mixture. The reaction mixture was heated under reflux for 24 h. The mixture was cooled to room temperature and the solvent removed under reduced pressure. Water (5 mL) and ether (5 mL) were added to the mixture and the layers separated. The aqueous layer was further extracted with ether (3 × 5 mL). The organic extracts were combined, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography on silica gel to give the bis-alkene.

(*S*)-(+)-1-Benzyloxy-*N*-but-3-enyl-2-but-3-enylamine (*S*)-10. Obtained from N–O bond cleavage and subsequent *N*-alkylation of hydroxylamine (*S*,*S*)-**2b** (0.47 mmol) and purification by column chromatography on silica gel eluting with light petroleum-ether (1:4) as a colourless oil (45%); (Found: MH^+, 232.1706. $C_{15}H_{21}NO + H$ requires 232.1701); $[\alpha]_D^{25} + 20.5$ (*c* 0.88, $CHCl_3$); ν_{max} (film)/cm^{-1} 3329 (NH), 3073, 3027, 2976, 2909, 2853, 1639, 1450, 1352, 1091, 994, 907, 738, 697; δ_H (300 MHz; $CDCl_3$) 7.31 (5 H, m, ArH), 5.86 – 5.57 (2 H, m, 2 × =CH), 5.29–4.94 (4 H, m, 2 × $=CH_2$), 4.52 (2 H, s, CH_2Ph), 3.51 – 3.29 (3 H, m, OCH_2, NCH), 2.72 (1 H, dt, *J* 11.3, 7.2, NC*H*H), 2.54 (1 H, dt, *J* 11.3, 7.0, NCH*H*), 2.26 (2 H, m, CH_2CH=), 1.86 (1 H, br s, NH); δ_C (75 MHz; $CDCl_3$) 138.6 (C), 138.3 (CH), 136.9 (CH), 128.8 (CH), 128.09 (CH), 128.07 (CH), 118.0 (CH_2), 116.7 (CH_2), 73.8 (CH_2), 73.6 (CH_2), 61.9 (CH), 46.8 (CH_2), 34.8 (CH_2); *m*/*z* (CI) 232 (MH^+, 41%), 164 (49), 152 (100), 149 (42).

(*R*)-(−)-1-Benzyloxy-*N*-but-3-enyl-2-but-3-enylamine (*R*)-10. Obtained from N–O bond cleavage and subsequent *N*-alkylation of hydroxylamine (*R*,*R*)-**2b** (4.62 mmol) and purification by column chromatography on silica gel eluting with light petroleum-ether (1:3) as a colourless oil (50%); $[\alpha]_D^{25} - 21.1$ (*c* 0.95, $CHCl_3$); *Spectroscopic properties identical to the* (*S*)-*enantiomer* (*S*)-**10**.

(*S*)-(+)-1-Benzyloxy-*N*-but-3-enyl-2-pent-4-enylamine 11. Obtained from N–O bond cleavage and subsequent *N*-alkylation of hydroxylamine **2e** (0.47 mmol) and purification by column chromatography on silica gel eluting with light petroleum-ether (1:2) as a colourless oil (47%); (Found: M^+, 245.1770. $C_{16}H_{23}NO$ requires 245.1780); $[\alpha]_D^{22} + 3.2$ (*c* 1.24, $CHCl_3$); ν_{max} (film)/cm^{-1} 3329 (NH), 3073, 3027, 2914, 2848, 1634, 1475, 1358, 1204, 1096, 994, 907, 738, 702; δ_H (300 MHz; $CDCl_3$) 7.32 (5 H, m, ArH), 5.78 (2 H, m, 2 × =CH), 5.07 (4 H, m, 2 × $=CH_2$), 4.52 (2 H, s, CH_2Ph), 3.43 (2 H, m, OCH_2), 2.82 (1 H, m, NCH), 2.69 (2 H, m, NCH_2), 2.23 (4 H, m, 2 × CH_2CH=), NH signal not observed; δ_C (75 MHz; $CDCl_3$) 138.8 (C), 136.8 (CH), 135.7 (CH), 128.8 (CH), 128.04 (CH), 127.99 (CH), 117.7 (CH_2), 116.8 (CH_2), 73.6 (CH_2), 72.7 (CH_2), 57.3 (CH), 46.8 (CH_2), 36.6 (CH_2), 34.9 (CH_2); *m*/*z* (EI) 245 (M^+, 4%), 219 (5), 204 (79), 124 (100), 98 (5), 91 (44), 82 (12), 65 (13), 55 (26).

General procedure for the preparation of Cbz-protected secondary amines 12/13

The pure secondary amine **10/11** was dissolved in THF-water (20 mL, 1:1) and sodium carbonate (1.52 mmol) was added. The solution was cooled to 0 °C and benzyl chloroformate (0.50 mmol) added dropwise. The mixture was allowed to warm to room temperature and stirred overnight. The THF was evaporated under reduce pressure. Ether (10 mL) was added, the layers were separated, and the aqueous layer was extracted with further portions of ether (3x). The organic layers were combined, dried ($MgSO_4$), filtered and evaporated.

(*S*)-(+)-1-Benzyloxy-*N*-benzyloxycarbonyl-*N*-but-3-enyl-2-but-3-enylamine 12. Obtained from the Cbz-protection of amine (*S*)-**10** (0.16 mmol) and purification by column chromatography on silica gel eluting with ether-light petroleum (1:2) as a yellow oil (80%); (Found: MH^+, 366.2068. $C_{23}H_{27}NO_3 + H$ requires 366.2069); $[\alpha]_D^{25} + 8.9$ (*c* 1.02, $CHCl_3$); ν_{max} (film)/cm^{-1} 3063, 3027, 2976, 2935, 2858, 1696 (C=O), 1634, 1501, 1455, 1409, 1286, 1255, 1102, 989, 912, 738, 687; δ_H (400 MHz; C_6D_6, 80 °C) 7.36 – 7.11 (10 H, m, ArH), 5.96 (1 H, m, =CH), 5.78 (1 H, m, =CH), 5.21 (2 H, s, CH_2Ph), 5.19 – 4.98 (4 H, m, 2 × $=CH_2$), 4.71 (1 H, q, *J* 6.0, NCH), 4.39 (2 H, AB, *J* 12.1, CH_2Ph), 3.75 (1 H, t, *J* 8.1, OC*H*H), 3.61 (1 H, dd, *J* 9.8, 5.7, OCH*H*), 3.40 (2 H, m, NCH_2), 2.45 (2 H, m, NCH_2CH_2); δ_C (100 MHz; C_6D_6, 80 °C) 155.8 (C), 138.6 (C), 137.5 (C), 135.7 (CH), 135.3 (CH), 128.3 – 127.4 (6 × CH), 116.6 (CH_2), 115.8 (CH_2), 73.0 (CH_2), 70.9 (CH_2), 66.8 (CH_2), 59.6 (CH), 46.0 (CH_2), 34.1 (CH_2); *m*/*z* (ES) 748 (2 M + NH_4, 30%), 383 (M + NH_4, 66), 366 (MH^+, 100).

(*S*)-(+)-1-Benzyloxy-*N*-benzyloxycarbonyl-*N*-but-3-enyl-2-pent-4-enylamine 13. Obtained from the Cbz-protection of amine **11** (0.22 mmol) and purification by column chromatography on silica gel eluting with ether-light petroleum (1:4) as a yellow oil (81%); (Found: MH^+, 380.2236. $C_{24}H_{29}NO_3 + H$ requires 380.2226); $[\alpha]_D^{22}$ +5.9 (*c* 1.02, $CHCl_3$); ν_{max} (film)/cm^{-1} 3068, 3032, 2971, 2935, 2858, 1696 (C=O), 1450, 1419, 1286, 1219, 1107, 994, 912, 738; δ_H (400 MHz; C_6D_6, 80 °C) 7.26 (10 H, m, ArH), 5.76 (2 H, m, 2 × =CH), 5.17 (2 H, s, CH_2Ph), 5.07 (2 H, d, *J* = 17.2 Hz, 2 × =C*H*H), 5.01 (2 H, d, *J* 10.2, 2 × =CH*H*), 4.37 (2 H, AB, *J* 12.0, CH_2Ph), 4.16 (1 H, m, NCH), 3.65 (1 H, br, OC*H*H), 3.49 (1 H, br, OCH*H*), 3.37 (2 H, t, *J* 7.6, NCH_2), 2.41 (4 H, m, 2 × CH_2CH=); δ_C (100 MHz; C_6D_6, 80 °C) 155.8 (C), 138.7 (C), 137.6 (C), 135.9 (CH), 135.3 (CH), 128.22 (CH), 128.20 (CH), 127.9 (CH), 127.7 (CH), 127.5 (CH), 127.4 (CH), 116.6 (CH_2), 115.7 (CH_2), 73.0 (CH_2), 71.3 (CH_2), 66.7 (CH_2), 57.8 (CH), 46.0 (CH_2), 34.6 (CH_2), 34.1 (CH_2); *m*/*z* (CI) 380 (MH^+, 19%), 336 (35), 294 (35), 272 (31), 258 (21), 214 (17), 202 (15), 181 (34), 91 (100).

(2*R*,2′*S*)-(−)-1-Benzyloxy-*N*-(but-3-enyl)-*N*-(2-*tert*-butyloxycarbonylamino-3-methylpentanoyl)-2-but-3-enylamine 14. (*S*)-*N*-Boc-isoleucine (109 mg, 0.47 mmol), 1-hydroxybenzotriazole (64 mg, 0.47 mmol) and (*R*)-(−)-1-benzyloxy-*N*-but-3-enyl-2-but-3-enylamine (*R*)-**10** (100 mg, 0.43 mmol) were added successively to dichloromethane (8 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature for 15 min and then re-cooled to 0 °C. *N*,*N*′-Dicyclohexylcarbodiimide (97 mg, 0.47 mmol) was added at this temperature and the solution was allowed to warm to room temperature and stirred overnight. The solution was filtered and evaporated. The crude product was directly purified by column chromatography on silica gel eluting with diethyl ether–light petroleum (1 : 3) to give the *title compound* (86 mg, 45%) as a colourless oil; (Found: MH^+, 445.3076. $C_{26}H_{40}N_2O_4 + H$ requires 445.3066); $[\alpha]_D^{23}$ −20.0 (*c* 0.60, $CHCl_3$); ν_{max} (film)/cm^{-1} 3426, 3310 (NH), 3079, 2968, 2933, 2876, 1712 (C=O), 1636 (C=O), 1497, 1456, 1420, 1366, 1248, 1172, 1114, 1017, 919, 735; δ_H (400 MHz; d_6-DMSO, 120 °C) 7.31 (5 H, m, ArH), 6.11–5.72 (3 H, m, 2 × =CH, NH), 5.20 (2 H, m, $=CH_2$), 5.03 (2 H, m, $=CH_2$), 4.75 (1 H, br m, NCH), 4.53 (2 H, AB, *J* = 12.0 Hz, CH_2Ph), 4.29 (1 H, t, *J* 8.0, NC*H*CH), 3.73 (2 H, m, OCH_2), 3.37 (2 H, m, NCH_2), 2.43–2.19 (2 H, br m, CH_2), 1.81 (1 H, br, NCHC*H*), 1.50 (1 H, br m, C*H*H), 1.40 (9 H, s, CMe_3), 1.11 (1 H, m, CH*H*), 0.82 (6 H, m, 2 × Me); δ_C (75 MHz; $CDCl_3$) *two rotamers* 173.0 (C), 172.7 (C), 155.6 (C), 138.0 (C), 137.5 (C), 135.7 (CH), 134.5 (CH), 134.3 (CH), 133.7 (CH), 128.42 (CH), 128.35 (CH), 127.84 (CH), 127.79 (CH), 127.6 (CH), 118.2 (CH_2), 117.5 (CH_2), 116.1 (CH_2), 79.29 (C), 79.25 (C), 73.3 (CH_2), 73.1 (CH_2), 70.3 (CH_2), 69.6 (CH_2), 59.3 (CH), 58.5 (CH), 55.1 (CH), 54.6 (CH), 47.0 (CH_2), 42.6 (CH_2), 38.9 (CH), 37.8 (CH), 34.5 (CH_2), 32.9 (CH_2), 28.3 (Me), 24.1 (CH_2),

23.8 (CH_2), 15.9 (Me), 15.7 (Me), 11.34 (Me), 11.25 (Me), the spectrum shows two signals for every C, with the exception of one C=O, ArCH, =CH_2 and Me for which only one peak is observed; *m/z* (CI) 445 (MH^+, 27%), 389 (89), 371 (24), 345 (100), 303 (17), 259 (13), 232 (42), 190 (13), 130 (12).

General procedure for ring-closing metathesis

The diene (0.470 mmol) was dissolved in dry dichloromethane (4 mL) under nitrogen. To the solution was added benzylidene-bis-(tricyclohexylphosphine)dichlororuthenium (38.7 mg, 0.047 mmol, 10 mol%) (Grubbs' catalyst) and the mixture stirred until complete consumption of starting material was observed by TLC. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel eluting with diethyl ether–light petroleum to give the corresponding heterocycle.

(*S*)-(−)-*N*-Benzyloxycarbonyl-2-benzyloxymethyl-2,5-dihydropyrrole 15. Obtained from the ring-closing metathesis of bis-alkene **8** (0.38 mmol) after purification by column chromatography on silica gel eluting diethyl ether–light petroleum (1 : 2) as a colourless oil (96%); (Found: MH^+, 324.1598. $C_{20}H_{21}NO_3$ + H requires 324.1599); $[\alpha]_D^{25}$ −158.3 (*c* 0.84, $CHCl_3$); ν_{max} (film)/cm^{-1} 3088, 3058, 3027, 2945, 2899, 2858, 1706 (C=O), 1624, 1496, 1455, 1414, 1358, 1317, 1199, 1102, 1004, 733, 697; δ_H (400 MHz; C_6D_6, 80 °C) 7.42–7.13 (10 H, m, ArH), 5.72 (1 H, m, =CH), 5.45 (1 H, m, =CH), 5.21 (2 H, AB, *J* = 12.5 Hz, C*H*$_2$Ph), 4.77 (1 H, br, NCH), 4.41 (2 H, s, C*H*$_2$Ph), 4.17 (1 H, br, C*H*H), 4.06 (1 H, br, CH*H*), 3.84 (1 H, br, C*H*H), 3.67 (1 H, br, CH*H*); δ_C (100 MHz; C_6D_6, 80 °C) 154.2 (C), 139.0 (C), 137.5 (C), 128.8 (CH), 128.4 (CH), 128.3 (CH), 128.1 (CH), 127.9 (CH), 127.4 (CH), 127.3 (CH), 125.6 (CH), 73.3 (CH_2), 71.4 (CH_2), 66.6 (CH_2), 64.5 (CH), 53.9 (CH_2); *m/z* (CI) 324 (MH^+, 100%), 202 (10), 190 (85), 158 (16), 143 (10), 126 (10), 108 (48), 91 (72), 82 (52), 68 (44).

(*S*)-(+)-*N*-Benzyloxycarbonyl-2-benzyloxymethyl-1,2,3,6-tetrahydropyridine 16. Obtained from the ring-closing metathesis of bis-alkene **9** (0.21 mmol) after purification by column chromatography on silica gel eluting diethyl ether–light petroleum (1 : 2) as a colourless oil (84%); (Found: MH^+, 338.1756. $C_{21}H_{23}NO_3$ + H requires 338.1756); $[\alpha]_D^{23}$ +7.5 (*c* 0.53, $CHCl_3$); ν_{max} (film)/cm^{-1} 3068, 3037, 2899, 2853, 1696 (C=O), 1450, 1414, 1347, 1219, 1102, 1015, 743; δ_H (400 MHz; C_6D_6, 80 °C) 7.25 (10 H, m, ArH), 5.50 (1 H, m, =CH), 5.38 (1 H, m, =CH), 5.25 (2 H, s, C*H*$_2$Ph), 4.86 (1 H, br, NCH), 4.39 (3 H, m, C*H*$_2$Ph, OC*H*H), 3.53 (2 H, m, OCH*H*, NC*H*H), 3.33 (1 H, dd, *J* = 7.3 Hz, NCH*H*), 2.23 (1 H, m, NCHC*H*H), 1.92 (1 H, m, NCHCH*H*); δ_C (100 MHz; C_6D_6, 80 °C) 155.6 (C), 138.9 (C), 137.6 (C), 128.25 (CH), 128.17 (CH), 127.9 (CH), 127.7 (CH), 127.4 (CH), 127.3 (CH), 123.4 (CH), 122.6 (CH), 72.8 (CH_2), 69.2 (CH_2), 66.9 (CH_2), 48.0 (CH), 40.7 (CH_2), 25.4 (CH_2); *m/z* (CI) 355 (M + NH_4, 3%), 338 (MH^+, 50), 294 (5), 216 (10), 204 (100), 157 (15), 140 (12), 108 (40), 91 (56), 82 (57).

(*S*)-(−)-*N*-Benzyloxycarbonyl-2-benzyloxymethyl-1,2,5,6-tetrahydropyridine 17. Obtained from the ring-closing metathesis of bis-alkene **12** (0.12 mmol) after purification by column chromatography on silica gel eluting diethyl ether–light petroleum (1 : 2) as a colourless oil (93%); (Found: MH^+, 338.1755. $C_{21}H_{23}NO_3$ + H requires 338.1756); $[\alpha]_D^{23}$ −173.2 (*c* 0.71, $CHCl_3$); ν_{max} (film)/cm^{-1} 3088, 3058, 3027, 2925, 2894, 2848, 1701 (C=O), 1496, 1450, 1424, 1363, 1327, 1276, 1250, 1194, 1107, 1025, 738, 697; δ_H (400 MHz; C_6D_6, 80 °C) 7.36–7.10 (10 H, m, ArH), 5.69 (2 H, m, HC=CH), 5.23 (2 H, AB, *J* = 12.4 Hz, C*H*$_2$Ph), 4.83 (1 H, br, NCH), 4.41 (2 H, AB, *J* 12.1, C*H*$_2$Ph), 4.29 (1 H, br, NC*H*H), 3.54 (2 H, d, *J* 5.3, OCH_2), 2.99 (1 H, m, NCH*H*), 2.07 (1 H, m, NCH_2C*H*H), 1.63 (1 H, m, NCH_2CH*H*); δ_C (100 MHz; C_6D_6, 80 °C) 155.0 (C), 138.8 (C), 137.6 (C), 128.2 (CH), 127.9 (CH), 127.7 (CH), 127.42 (CH), 127.37 (CH), 127.3 (CH), 126.3 (CH), 126.2 (CH), 73.1 (CH_2), 71.6 (CH_2), 66.9 (CH_2), 52.2 (CH), 38.2 (CH_2), 24.8 (CH_2); *m/z* (CI) 355 (M + NH_4, 3%), 338 (MH^+, 85), 294 (6), 246 (5), 216 (15), 204 (100), 172 (20), 157 (13), 140 (12), 108 (38), 91 (69), 82 (79).

(*S*)-(−)-*N*-Benzyloxycarbonyl-2-benzyloxymethyl-2,3,6,7-tetrahydro-1*H*-azepine 18. Obtained from the ring-closing metathesis of bis-alkene **13** (0.17 mmol) after purification by column chromatography on silica gel eluting diethyl ether–light petroleum (1 : 1) as a colourless oil (85%); (Found: MH^+, 352.1910. $C_{22}H_{25}NO_3$ + H requires 352.1912); $[\alpha]_D^{25}$ −93.1 (*c* 1.02, $CHCl_3$); ν_{max} (film)/cm^{-1} 3083, 3058, 3022, 2935, 2889, 2853, 1696 (C=O), 1450, 1419, 1363, 1327, 1260, 1199, 1020, 733, 692; δ_H (400 MHz; C_6D_6, 80 °C) 7.37–7.12 (10 H, m, ArH), 5.55 (1 H, m, =CH), 5.46 (1 H, m, =CH), 5.21 (2 H, AB, *J* = 12.5 Hz, C*H*$_2$Ph), 4.58 (1 H, br, NCH), 4.40 (2 H, s, C*H*$_2$Ph), 3.85 (1 H, br, C*H*H), 3.53 (2 H, br, CH_2), 3.42 (1 H, m, CH*H*), 2.67–2.43 (2 H, br, C*H*H, C*H*H), 2.16 (1 H, m, CH*H*), 2.01 (1 H, m, CH*H*); δ_C (100 MHz; C_6D_6, 80 °C) 155.9 (C), 138.9 (C), 137.7 (C), 129.6 (CH), 128.3–127.1 (6 × CH), 124.9 (CH), 73.1 (CH_2), 72.0 (CH_2), 66.8 (CH_2), 55.5 (CH), 40.7 (CH_2), 31.0 (CH_2), 28.1 (CH_2); *m/z* (CI) 352 (MH^+, 45%), 330 (8), 218 (100), 186 (13), 171 (20), 154 (19), 106 (60), 96 (83), 91 (66), 52 (19).

(2*R*,2′*S*)-(+)-2-Benzyloxymethyl-1-(2-*tert*-butyloxycarbonylamino-3-methylpentanoyl)-1,2,5,6-tetrahydropyridine 19. Obtained from the ring-closing metathesis of bis-alkene **14** (0.59 mmol) after purification by column chromatography on silica gel eluting diethyl ether–light petroleum (1 : 2 to 1 : 1) as a yellow oil (97%); (Found: MH^+, 416.2680. $C_{24}H_{35}N_2O_4$ + H requires 416.2675); $[\alpha]_D^{23}$ +160.0 (*c* 0.70, $CHCl_3$); ν_{max} (film)/cm^{-1} 3416, 3291 (NH), 3032, 2967, 2931, 2863, 1701 (C=O), 1635 (C=O), 1497, 1455, 1391, 1365, 1304, 1244, 1171, 1116, 1043, 737, 699; δ_H (400 MHz; DMSO, 120 °C) 7.31 (5 H, m, ArH), 6.08 (1 H, br d, *J* = 7.3 Hz, NH), 5.91 (1 H, m, =CH), 5.75 (1 H, m, =CH), 4.85 (1 H, br, NC*H*CH=), 4.53 (2 H, AB, *J* 12.4, C*H*$_2$Ph), 4.31 (1 H, t, *J* 8.6, NCH), 4.19 (1 H, br, NC*H*H), 3.60 (2 H, m, OCH_2), 2.87 (1 H, br, NCH*H*), 2.22–2.00 (1 H, m, NC*H*$_2$CH=), 1.82 (1 H, br, C*H*Me), 1.52 (1 H, m, C*H*H), 1.40 (9 H, s, CMe_3), 1.12 (1 H, m, CH*H*), 0.84 (6 H, m, 2 × Me); δ_C (75 MHz; $CDCl_3$) *two rotamers* 172.1 (C), 170.8 (C), 155.9 (C), 155.5 (C), 138.2 (C), 137.8 (C), 128.39 (CH), 128.35 (CH), 127.8 (CH), 127.7 (CH), 127.52 (CH), 127.49 (CH), 126.4 (CH), 125.7 (CH), 124.9 (CH), 79.4 (C), 79.3 (C), 73.2 (CH_2), 73.1 (CH_2), 70.8 (CH_2), 70.4 (CH_2), 54.8 (CH), 58.7 (CH), 53.7 (CH), 50.7 (CH), 40.8 (CH_2), 38.1 (CH), 37.3 (CH), 35.5 (CH_2), 28.34 (Me), 28.27 (Me), 25.7 (CH_2), 24.7 (CH_2), 24.1 (CH_2), 23.6 (CH_2), 16.1 (Me), 15.7 (Me), 11.6 (Me), 11.0 (Me); only three peaks for the two =CH of both rotamers; *m/z* (EI) 416 (M^+, 3%), 360 (4), 343 (7), 295 (8), 221 (84), 195 (15), 130 (26), 91 (90), 82 (100).

Reduction and deprotection of tetrahydropyridines

(*S*)-(+)-Piperidine-2-methanol hydrochloride 20. Tetrahydropyridine **17** (32 mg, 0.095 mmol) was dissolved in methanol (1 mL) and hydrochloric acid (1 M; 1 mL) and hydrogenated over palladium on charcoal (10% w/w; 20 mg) overnight. The catalyst was filtered through Celite and the solvent was removed *in vacuo* to give the piperidine **20** as a yellow solid (15 mg, quantitative yield); mp 126–128 °C (lit.,[34] for the racemate, mp 130–132 °C); (Found: MH^+, 116.1069. $C_6H_{13}NO$ + H requires 116.1075); $[\alpha]_D^{24}$ +5.8 (*c* 1.2, MeOH); ν_{max} (KBr)/cm^{-1} 3380, 3191, 2997, 2948, 2879, 2781, 2752, 2558, 2530, 2448, 2413, 1598, 1452, 1428, 1401, 1324, 1051, 1023, 912; δ_H (300 MHz; MeOD) 3.78 (1 H, dd, *J* = 11.8, 3.8 Hz, OC*H*H), 3.59 (1 H, dd, *J* 11.8, 7.0, OCH*H*), 3.37 (1 H, br m, NC*H*H), 3.20 (1 H, br, NCH), 3.02 (1 H, br m, NCH*H*), 2.00–1.48 (6 H, m, 3 × CH_2); OH and NH not observed; δ_C (75 MHz; MeOD) 64.0 (CH_2),

60.5 (CH), 46.5 (CH_2), 27.0 (CH_2), 24.3 (CH_2), 23.7 (CH_2); *m/z* (CI) 116 (MH^+, 100%), 114 (17), 98 (28), 84 (11).

(2*R*,2′*S*)-(+)-1-(2-*tert*-Butyloxycarbonylamino-3-methylpentanoyl)piperidine-2-methanol 21. Tetrahydropyridine **19** (220 mg, 0.53 mmol) was dissolved in methanol (8 mL) and hydrogenated over palladium on charcoal (10% w/w; 70 mg) overnight. The catalyst was filtered through Celite and the solvent was removed *in vacuo* to give the piperidine **21** after purification by column chromatography on silica gel eluting with diethyl ether as a colourless sticky oil (quantitative yield); (Found: MH^+, 329.2446. $C_{17}H_{32}N_2O_4$ + H requires 329.2440); $[\alpha]_D^{26}$ +43.9 (*c* 0.41, $CHCl_3$); ν_{max} (film)/cm^{-1} 3416, 3327, 2965, 2936, 2875, 1701 (C=O), 1625 (C=O), 1521, 1446, 1391, 1366, 1248, 1172, 1046, 1020; δ_H (400 MHz; DMSO, 120 °C) 6.04 (1 H, br, NH), 4.45–4.18 (2 H, m, 2 × NCH), 4.00 (1 H, br, NC*H*H), 3.58 (2 H, m, OCH_2), 1.78 (2 H, m, NCHC*H*, C*H*H), 1.70–1.23 (15 H, m, CH*H*, 2 × CH_2, C*H*, CMe_3), 1.10 (1 H, m, CH*H*), 0.84 (6 H, m, 2 × Me); OH and NCH*H* not observed; δ_C (100 MHz; DMSO, 120 °C) 171.2 (C), 155.7 (C), 78.7 (C), 60.0 (CH_2), 55.0 (CH), 37.0 (CH), 28.7 (Me), 25.6 (2 × CH_2), 24.5 (CH_2), 19.4 (CH_2), 16.2 (Me), 11.3 (Me); NCH and NCH_2 signals not observed, probably due to extreme broadening by *J*-coupling to N; *m/z* (CI) 329 (MH^+, 8%), 311 (5), 273 (52), 255 (19), 229 (100), 116 (14).

4-Bromobenzoate derivative: (2*R*,2′*S*)-(−)-2-(4-bromobenzoyloxymethyl)-1-(2-*tert*-butoxycarbonylamino-3-methylpentanoyl)piperidine. To a solution of alcohol **21** (45 mg, 0.14 mmol), triethylamine (0.02 mL, 0.14 mmol) and DMAP (cat.) in dichloromethane (2 mL), 4-bromobenzoyl chloride (31 mg, 0.14 mmol) was added and the reaction mixture was stirred overnight. The solvent was evaporated and after purification by column chromatography on silica gel eluting with diethyl ether–light petroleum (1 : 1) the title compound was obtained (59 mg, 84%) as a colourless sticky oil; (Found: MH^+, 511.1806. $C_{24}H_{35}{}^{79}BrN_2O_5$ + H requires 511.1808); $[\alpha]_D^{24}$ +4.0 (*c* 0.99, $CHCl_3$); ν_{max} (film)/cm^{-1} 3432, 3314, 2966, 2930, 2868, 1718 (C=O), 1636 (C=O), 1588 1496, 1437, 1368, 1267, 1173, 1107, 1012; δ_H (400 MHz; DMSO, 120 °C) 7.83 (2 H, m, ArH), 7.67 (2 H, m, ArH), 6.07 (1 H, br, NH), 4.86 (1 H, br, NCH), 4.56 (1 H, br, OC*H*H), 4.40 (1 H, dd, *J* = 11.2, 6.1 Hz, OCH*H*), 4.28 (1 H, t, *J* 8.2, NCH), 4.02 (1 H, br, NC*H*H), 1.85–1.27 (17 H, m, NCHC*H*, C*H*H, 3 × CH_2, CMe_3), 1.10 (1 H, m, CH*H*), 0.80 (6 H, m, 2 × Me); the NCH*H* signal is missing and is probably under the solvent signal; δ_C (100 MHz; DMSO, 120 °C) 171.4 (C), 165.4 (C), 155.6 (C), 132.2 (CH), 131.5 (CH), 129.6 (C), 127.6 (C), 78.7 (C), 63.2 (CH_2), 55.0 (CH), 37.1 (CH), 28.6 (Me), 26.0 (CH_2), 25.6 (CH_2), 24.4 (CH_2), 19.5 (CH_2), 16.2 (Me), 11.2 (Me); the NCH and NCH_2 signals are not observed, probably due to extreme broadening by *J*-coupling to N; *m/z* (CI) 513/511 (MH^+, 30%), 457/455 (22), 413/411 (100), 311 (14), 300/298 (14), 211 (24), 203/201 (24).

(2*S*,3*R*,4*S*)-(−)-1-Benzyloxycarbonyl-2-benzyloxymethyl-3,4-diacetoxypyrrolidine 22. Dihydropyrrole **15** (100 mg, 0.31 mmol) was dissolved in acetone–water (2 : 1; 6 mL) and 4-methylmorpholine *N*-oxide (72 mg, 0.62 mmol) was added followed by one crystal of osmium tetroxide. After stirring for 2 d the solution was cooled to 0 °C and a saturated aqueous solution of $NaHSO_3$ (6 mL) was added and warmed to room temperature. The mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was dissolved in dichloromethane (5 mL) at room temperature and pyridine (0.10 mL, 1.24 mmol) and acetic anhydride (0.12 mL, 1.24 mmol) were added. The mixture was stirred overnight and then concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel eluting ethyl acetate–light petroleum (1 : 4) to give the *title compound* (115 mg, 84%) as a colourless oil; (Found: MH^+, 442.1878. $C_{24}H_{27}NO_7$ + H requires 442.1866); $[\alpha]_D^{25}$ −24.1 (*c* 0.83, $CHCl_3$); ν_{max} (film)/cm^{-1} 3063, 3032, 2950, 2894, 2858, 1750 (C=O), 1707 (C=O), 1455, 1418, 1356, 1244, 1093, 1027, 740, 699; δ_H (400 MHz; DMSO, 120 °C) 7.32 (10 H, m, ArH), 5.42 (2 H, m, 2 × OCH), 5.12 (2 H, AB, *J* = 13.2 Hz, CH_2Ph), 4.50 (2 H, AB, *J* 12.3, CH_2Ph), 3.96 (1 H, m, NCH), 3.75 (2 H, m, OC*H*H, NC*H*H), 3.66 (1 H, dd, *J* 10.0, 2.3, OCH*H*), 3.50 (1 H, m, NC*H*H), 2.03 (3 H, s, Me), 2.01 (3 H, s, Me); δ_C (100 MHz; DMSO, 120 °C) 169.8 (C), 169.7 (C), 154.4 (C), 138.6 (C), 137.2 (C), 128.8 (CH), 128.6 (CH), 128.2 (CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 73.8 (CH), 73.2 (CH_2), 70.2 (CH), 68.7 (CH_2), 66.9 (CH_2), 61.8 (CH), 49.2 (CH_2), 20.7 (Me), 20.6 (Me); *m/z* (CI) 442 (MH^+, 100%), 398 (69), 244 (21), 181 (38), 91 (62).

1,4-Dideoxy-1,4-imino-D-ribitol hydrochloride 23. Pyrrolidine **22** (101 mg, 0.23 mmol) was dissolved in methanol (3 mL) and hydrochloric acid (1 M; 2 mL) and hydrogenated over palladium on charcoal (10% w/w; 20 mg) overnight. The catalyst was filtered through Celite and the solvent was removed *in vacuo* to give the title compound **23** as a yellow solid (36 mg, quantitative yield); mp 124–125 °C (lit.,[28] mp 128–132 °C); (Found: MH^+, 134.0817. $C_5H_{11}NO_3$ + H requires 134.0817); $[\alpha]_D^{25}$ +53.3 (*c* 0.75, H_2O) {lit.,[28] $[\alpha]_D^{20}$ +57.6 (*c* 0.59, H_2O)} {lit.,[30] $[\alpha]_D^{20}$ +53.9 (*c* 1, H_2O)}; δ_H (400 MHz; D_2O) 4.36 (1 H, m, NCH_2CHOH), 4.19 (1 H, dd, *J* = 8.5, 4.0 Hz, NCHC*H*OH), 3.94 (1 H, dd, *J* 12.6, 2.6, C*H*HOH), 3.80 (1 H, dd, *J* 12.6, 6.0, CH*H*OH), 3.59 (1 H, m, NCH), 3.48 (1 H, dd, *J* 13.0, 4.0, NC*H*H), 3.34 (1 H, m, NCH*H*); δ_C (75 MHz; D_2O) 72.2 (CH), 70.4 (CH), 62.8 (CH), 59.0 (CH_2), 50.7 (CH_2); *m/z* (CI) 134 (MH^+, 100%), 116 (20), 98 (18).

Acknowledgements

We thank the EPSRC for support of this work (studentships to T. S. C. and A. S. L.), GlaxoSmithKline for a CASE award (to T. S. C.), and the EPSRC Mass Spectrometry Centre at Swansea for mass spectra, and the EPSRC Chemical Database Service at Daresbury.[35]

References

1 Part 6: T. S. Cooper, P. Laurent, C. J. Moody and A. K. Takle, *Org. Biomol. Chem.*, 2004, **2**, 265.
2 D. Enders and U. Reinhold, *Tetrahedron: Asymmetry*, 1997, **8**, 1895.
3 R. Bloch, *Chem. Rev.*, 1998, **98**, 1407.
4 P. Merino, S. Franco, F. L. Merchan and T. Tejero, *Synlett*, 2000, 442.
5 J. P. Adams, *J. Chem. Soc., Perkin Trans. 1*, 2000, 125.
6 J. A. Ellman, *Pure Appl. Chem.*, 2003, **75**, 39.
7 P. Zhou, B. C. Chen and F. A. Davis, *Tetrahedron*, 2004, **60**, 8003.
8 C. J. Moody, *Chem. Commun.*, 2004, 1341.
9 Preliminary communication: T. S. Cooper, A. S. Larigo, P. Laurent, C. J. Moody and A. K. Takle, *Synlett*, 2002, 1730.
10 P. T. Gallagher, J. C. A. Hunt, A. P. Lightfoot and C. J. Moody, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2633.
11 D. Enders and H. Kempen, *Synlett*, 1994, 969.
12 J. C. A. Hunt, P. Laurent and C. J. Moody, *J. Chem. Soc., Perkin Trans. 1*, 2002, 2378.
13 J. C. A. Hunt, C. Lloyd, C. J. Moody, A. M. Z. Slawin and A. K. Takle, *J. Chem. Soc., Perkin Trans. 1*, 1999, 3443.
14 S. Cicchi, A. Goti, A. Brandi, A. Guarna and F. Desarlo, *Tetrahedron Lett.*, 1990, **31**, 3351.
15 A. R. Ritter and M. J. Miller, *J. Org. Chem.*, 1994, **59**, 4602.
16 For a related route to protected 1,2-aminoalcohols, see: T. P. Tang, S. K. Volkman and J. A. Ellman, *J. Org. Chem.*, 2001, **66**, 8772.
17 Y. Hamada, M. Shibata, T. Sugiura, S. Kato and T. Shioiri, *J. Org. Chem.*, 1987, **52**, 1252.
18 B. Falkiewicz, A. S. Kolodziejczyk, B. Liberek and K. Wisniewski, *Tetrahedron*, 2001, **57**, 7909.
19 H. Matsunaga, T. Ishizuka and T. Kunieda, *Tetrahedron*, 1997, **53**, 1275.
20 T. K. Chakraborty and A. Ghosh, *Tetrahedron Lett.*, 2002, **43**, 9691.
21 L. De Luca, G. Giacomelli, S. Masala and A. Porcheddu, *J. Org. Chem.*, 2003, **68**, 4999.

22 J. E. Harvey, M. N. Kenworthy and R. J. K. Taylor, *Tetrahedron Lett.*, 2004, **45**, 2467.
23 N. K. Gulavita, S. P. Gunasekera, S. A. Pomponi and E. V. Robinson, *J. Org. Chem.*, 1992, **57**, 1767.
24 H. G. J. Visser, R. J. M. Nolte, J. W. Zwikker and W. Drenth, *J. Org. Chem.*, 1985, **50**, 3133.
25 For a review of the synthesis of nitrogen-containing heterocycles by RCM reactions, see: A. Deiters and S. F. Martin, *Chem. Rev.*, 2004, **104**, 2199.
26 S. B. Singh, D. L. Zink, J. M. Liesch, R. T. Mosley, A. W. Dombrowski, G. F. Bills, S. J. Darkin-Rattray, D. M. Schmatz and M. A. Goetz, *J. Org. Chem.*, 2002, **67**, 815.
27 Isolation: N. Asano, K. Oseki, E. Tomioka, H. Kizu and K. Matsui, *Carbohydr. Res.*, 1994, **259**, 243.
28 For some other approaches, see refs. 29–30: G. W. J. Fleet and J. C. Son, *Tetrahedron*, 1988, **44**, 2637.
29 J. F. Witte and R. W. McClard, *Tetrahedron Lett.*, 1991, **32**, 3927.
30 R. Kumareswaran and A. Hassner, *Tetrahedron: Asymmetry*, 2001, **12**, 3409.
31 For the synthesis of functionalized pyrrolidines by RCM reaction, see: K. B. Lindsay, M. Y. Tang and S. G. Pyne, *Synlett*, 2002, 731.
32 A. Padwa, S. F. Hornbuckle, G. E. Fryxell and Z. J. J. Zhang, *J. Org. Chem.*, 1992, **57**, 5747.
33 Y. Konda, Y. Takahashi, S. Arima, N. Sato, K. Takeda, K. Dobashi, M. Baba and Y. Harigaya, *Tetrahedron*, 2001, **57**, 4311.
34 F. F. Blicke and C.-J. Lu, *J. Am. Chem. Soc.*, 1955, **77**, 29.
35 D. A. Fletcher, R. F. McMeeking and D. J. Parkin, *J. Chem. Inf. Comput. Sci.*, 1996, **36**, 746.